IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ibuprofen Max 400mg Film-coated Tablets
Ibuprofen
PA1186/022/002

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

This product was initially authorised under procedure number UK/H/4780/001-002/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 14 January 2019 under procedure number IE/H/0903/001-002/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1186/022/002
Marketing Authorisation Holder: Chefaro Ireland DAC

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

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

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Ibuprofen 200 mg and 400 mg Film-coated Tablets (PL 16028/0156-0157; UK/H/4780/001-002/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and The Czech Republic, Germany, Denmark, Finland, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Sweden and Slovakia as Concemed Member States (CMS).

These products can be obtained without a prescription at a pharmacy (legal classification P).

These applications were made under the Decentralised Procedure (DCP), according to Alticle 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Brufen 200 mg and 400 mg tablets (Abbott Scandinavia AB), which were granted marketing authorisations in Sweden on 14 March 1975.

Ibuprofen 200 mg and 400 mg Film-coated Tablets are indicated for short-term symptomatic treatment of mild to moderate pain, such as headache, dysmenonhea (period pain), dental pain, and fever and pain in the common cold. These products contain the active substance ibuprofen. Ibuprofen is a non-steroidal anti-inflammatmy drug (NSAID) with analgesic, anti-inflammatmy and anti-pyretic properties.

No non-clinical studies were conducted, which is acceptable given that these applications were based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence studies were perfmmed, which compared the pha macokinetics of the test products Ibuprofen200 mg a11d 400 mg Film-coated Tablets to those of the reference products Brufen200 mg and 400 mg tablets (Abbott Scandinavia AB). The bioequivalence studies were canied out in accordance with Good Clinical Practice (GCP).

The RMS has been assumed that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved at the end of procedme on 10 September 2013. After a subsequent national phase, marketing authorisations were granted in the UK on 10 October 2013.

II. QUALITY ASPECTS

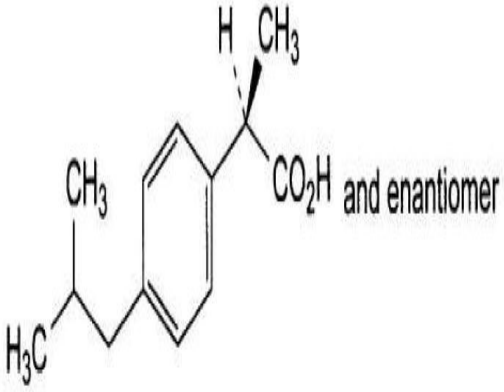
III.1 QUALITY ASPECTS

S. Active substance – Ibuprofen

rINN: Ibuprofen

Chemical name: (2RS)-2-[4-(2-Methylpropyl)phenyl]propanoic acid

Structure:



Molecular formula: $C_{13}H_{18}O_2$

Molecular weight: 206.3

Appearance: White or almost white crystalline powder or colourless crystals

Solubility: Practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates

All aspects of the manufacture and control of the active substance ibuprofen from its starting materials are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, as follows:

Tablet core:

For the 200 mg Film-coated Tablets: hypromellose, lactose monohydrate, magnesium stearate, maize starch, sodium starch glycolate (Type A), colloidal anhydrous silica

For the 400 mg Film-coated Tablets: croscarmellose sodium, lactose monohydrate, magnesium stearate, maize starch, povidone, colloidal anhydrous silica, talc

Film-coating:

Opadry-II White 85F18422 comprising macrogol 3350, poly(vinyl-alcohol), talc, titanium dioxide

With the exception of the Opadry-II White film-coating agent, all excipients used comply with their respective European Pharmacopoeia monographs. Opadry-II White film-coating complies with a suitable in-house specification, however, its individual constituents comply with their respective European Pharmacopoeia monographs.

With the exception of the lactose monohydrate, none of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

The milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

Pharmaceutical Development

The objective of the development programme was to formulate globally acceptable, stable and bioequivalent products that could be considered generic medicinal products of the currently licensed products, Brufen 200 mg and 400 mg tablets (Abbott Scandinavia AB).

A satisfactory account of the pharmaceutical development has been provided.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on three commercial-scale batches of each strength of finished product. The results are satisfactory.

Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System

The finished product is packaged in aluminium/polyvinylchloride (PVC) blister packs. Blisters are packaged in an outer cardboard carton in pack sizes of 6, 8, 10, 12, 16, 20, 24, 30, 48, 50, 96 and 100 tablets.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPCs, PILs and text versions of the labels are acceptable from a pharmaceutical perspective.

The results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for Ibuprofen 200mg sugar-coated tablets (PL 16028/0013; Galpharm Healthcare Limited) was provided. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains. As the PILs for Ibuprofen 200 mg and 400 mg Film-coated Tablets are consistent with the approved PIL for Ibuprofen 200mg sugar-coated tablets (PL 16028/0013) in their content and layout, additional readability testing is not deemed necessary.

Marketing Authorisation Application (MAA) form

The MAA forms are satisfactory from a pharmaceutical perspective.

Quality Overall Summary (Expert report)

The pharmaceutical expert report has been written by an appropriately qualified person summary of the pharmaceutical dossier.

Conclusion

The grant of Marketing Authorisations is recommended.

III. NON-CLINICAL ASPECTS

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are well-known, no further non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with 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.

IV. CLINICAL ASPECTS

Pharmacokinetics

In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence studies:

Study 1 - Ibuprofen 200 mg and 400 mg Sugar-Coated Tablets

As part of work to register the currently authorised sugar-coated formulations of the products (PL 16028/0028 and Pl 16028/0040) in Poland, a bioequivalence study was conducted to compare the pharmacokinetics of these products to those of the Polish reference product, as follows:

A balanced, open-label, randomised, three-treatment, six-sequence, three-period, single dose, three way crossover study comparing the pharmacokinetics of the test products Ibuprofen 400 mg Sugar-Coated Tablets (PL 16028/0040; Galpharm Healthcare Limited) and Ibuprofen 200 mg Sugar-Coated Tablets (PL 16028/0028; Galpharm Healthcare Limited) to those of the reference product Nurofen 200 mg Sugar-coated Tablets (Reckitt Benckiser Healthcare Sp.z.o.o., Poland) in healthy adult human subjects, under fasting conditions

Volunteers were given each treatment (1 x 400 mg tablet or 2 x 200 mg tablets) after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 12 hours post dose. Each regimen was separated by a washout period of 5 days.

A summary of the main pharmacokinetic results is presented in the table below:

Pharmacokinetic Parameters	Geometric mean		*(%)T/R	90% Confidence Interval
	Test (T1)	Reference (R)		
N	23	23	-	-
C_{max} (µg/ml)	28.99	32.24	89.77	83.89 - 96.06
AUC_{0-t} (hr.µg/ml)	121.98	120.41	101.26	97.46 - 105.21

Geometric mean, %T/R and 90% confidence intervals of ln-transformed pharmacokinetic parameters of Test (T2) and Reference formulation of Ibuprofen are summarized below:

Pharmacokinetic Parameters	Geometric mean		*(%)T/R	90% Confidence Interval
	Test (T2)	Reference (R)		
N	23	23	-	-
C_{max} (µg/ml)	34.57	32.24	106.99	99.98 - 114.49
AUC_{0-t} (hr.µg/ml)	121.09	120.41	100.42	96.65 - 104.34

*(%) T/R is ratio of TestGeoLSM/ RefGeoLSM.

Compared with the reference product, the 90 % confidence intervals for the test products are within 80.00-125.00 % for Cmax and AUC. It was concluded that ibuprofen 400 mg and 200 mg Sugar-coated Tablets are, therefore, bioequivalent with Nurofen 200 mg Sugar-coated Tablets.

The applicant requested a biowaiver to extrapolate the results of this bioequivalence study for sugar-coated tablets to the current applications for film-coated tablets. In support of this biowaiver request, comparative dissolution studies to demonstrate that the sugar-coated and film-coated products dissolve at similar rates were provided. However, as the dissolution studies did not adequately demonstrate equivalence between the sugar-coated and film-coated formulations for both strengths of product at each pH tested, the applicant was requested to submit further formal comparative bioequivalence studies between film-coated formulations of test and reference product. The following studies were, therefore, submitted:

Study 2 - Ibuprofen 200 mg Film-coated Tablets

A randomised, open-label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study comparing the pharmacokinetics of the test product Ibuprofen 200 mg Film-coated Tablets to those of the reference product Brufen 200 mg film-coated tablets (Abbott Scandanavia AB) in healthy adult human subjects, under fasting conditions.

Volunteers were given each treatment (a single dose of two 200 mg tablets) after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 12 hours post dose. Each regimen was separated by a washout period of 4 days.

A summary of the main pharmacokinetic results is presented in the table below:

Geometric least square mean (GeoLSM), %T/R and 90% confidence interval of ln-transformed pharmacokinetic parameters of Test (T) and Reference (R) product for ibuprofen are summarised below:

Pharmacokinetic Parameters	TestGeoLSM (T)	RefGeoLSM (R)	*T/R (%)	90% Confidence Interval
N	22	22	-	-
C_{max} (µg/ml)	34.3642	35.0285	98.10	88.62-108.60
AUC_{0-t} (hr.µg/ml)	111.6666	114.9646	97.13	94.37-99.97

Compared with the reference product, the 90 % confidence intervals for the test product are within 80.00-125.00 % for C_{max} and AUC. Ibuprofen 200 mg Film-coated Tablets are, therefore, considered bioequivalent with Brufen 200 mg tablets.

Study 2 - Ibuprofen 400 mg Film-coated Tablets

A randomised, open-label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study comparing the pharmacokinetics of the test product Ibuprofen 400 mg Film-coated Tablets to those of the reference product Brufen 400 mg film-coated tablets (Abbott Scandanavia AB) in healthy adult human subjects, under fasting conditions.

Volunteers were given each treatment (a single dose of one 400 mg tablet) after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 12 hours post dose. Each regimen was separated by a washout period of 4 days.

A summary of the main pharmacokinetic results is presented in the table below:

Treatment	AUC_τ µg/ml/h	C_{max} µg/ml	t_{max} h	$T_{1/2}$ h
Test	109.79	29.99	1.50	2.10
Reference	107.01	30.55	1.52	2.05
*Ratio (90% CI)	102.60 (99.67-105.62)	98.20 (91.94-104.87)		

AUC_∞ area under the plasma concentration-time curve from time zero to infinity
AUC_τ area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration (median)
$T_{1/2}$ half-life

**ln-transformed values*

Compared with the reference product, the 90 % confidence intervals for the test product are within 80.00-125.00 % for C_{max} and AUC. Ibuprofen 400 mg Film-coated Tablets are, therefore, considered bioequivalent with Brufen 400 mg tablets.

Efficacy

No new data on efficacy have been submitted and none are required for this type of application.

Safety

With the exception of the data submitted during the bioequivalence studies, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

SmPC, PIL and Labels

The SmPCs, PILs and text versions of the labels are acceptable from a clinical perspective.

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for these products.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion

The grant of Marketing Authorisations is recommended.

V. OVERALL CONCLUSIONS

QUALITY

The important quality characteristics of Ibuprofen 200 mg and 400 mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL

Bioequivalence has been demonstrated between the applicant's products and the reference products.

No new or unexpected safety concerns arose from these applications.

The SmPCs, PILs and text versions of labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant's products and the reference products. Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.

VI. REVISION DATE

18 February 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 UK/H/4780/001-002/DC to IE/H/903/001-002/DC			