LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ibetin
(ibuprofen)

SE/H/2057/01-02/DC

This module reflects the scientific discussion for the approval of Ibetin. The procedure was finalised on 2021-02-24. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

The application for Ibetin 200 mg and 400 mg, film-coated tablet is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Zentiva k.s., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following as concerned member states (CMS).

SE/H/2057/01/DC CMS: AT, BG, CZ, DK, FI, PL, SK
SE/H/2057/02/DC CMS: AT, BG, CZ, FI, SK, PL, ES, RO

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is:

SE/H/2057/01: Brufen, 200 mg, film-coated tablet authorised in SE since year 1975, with BGP Products AB as marketing authorisation holder.
SE/H/2057/02: Brufen, 400 mg, film-coated tablet authorised in SE since year 1975, with BGP Products AB as marketing authorisation holder.

The reference product used in the bioequivalence study is:

- Brufen, 400 mg, film-coated tablets from Sweden with BGP Products AB as marketing authorisation holder.
- Brufen, 200 mg, film-coated tablets, from Portugal with BGP Products, Unipessoal Lda as marketing authorisation holder.

European Reference Product (ERP)

A European Reference Product is used in

SE/H/2057/01/DC CMS DK, AT, FI, BG, CZ, PL and SK:
Brufen, 200 mg, film-coated tablet authorised in SE since year 1975, with BGP Products AB as marketing authorisation holder.
SE/H/2057/02/DC CMS FI, BG and PL:
Brufen, 400 mg, film-coated tablet authorised in SE since year 1975, with BGP Products AB as marketing authorisation holder.

The justification to use this product is based on RMS's own files.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Ibuprofen film-coated tablets with the reference product Brufen. The pivotal study was performed with the 800 mg strength, and an additional study was performed with a test batch of the 200 mg strength with the slowest observed dissolution in order to support the suggested dissolution specification.

Pharmacokinetic properties of the active substance

Absorption: Ibuprofen has an oral bioavailability of 80-90 %. Following an oral dose of ibuprofen maximal plasma concentrations occur at approximately 1-2 hours.

If administered with food, peak serum concentrations are lower and achieved more slowly than when taken on an empty stomach. Food does not affect markedly total bioavailability. In order to achieve a faster onset of action, the dose may be taken on an empty stomach. It is recommended that patients with sensitive stomachs take ibuprofen with food.

Linearity: The pharmacokinetics of ibuprofen is linear within the dose range 200-800 mg.

Elimination: The terminal half-life is 2 hours.

Study IBUPRL09206/ZNV-P0-163

Methods

This was a single-dose, two-way crossover study conducted in 22 healthy volunteers, comparing Ibuprofen, 800 mg, film-coated tablets with Brufen, 2x400 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 12 hours post-dose. Plasma concentrations of ibuprofen were determined with an HPLC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2019-03-15 and 2019-04-17.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for ibuprofen, n=20.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**238.851 ± 52.235**	**60.381 ± 10.468**	**1.63 (0.50-3.50)**
Reference	**235.235 ± 44.674**	**62.771 ± 14.540**	**1.63 (0.75-4.00)**
***Ratio (90% CI)**	**101.48 (98.53 – 104.51)**	**97.76 (89.77 – 104.30)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %. Comparable median and range for t_{max} was shown for the test and reference product.

A biowaiver was sought for the additional strengths of 200, 400, 600 mg.

Study IBUPRL27419/2020-4819
Since a decrease in dissolution rate was observed for all strengths of the drug product during the stability testing, an additional bioequivalence study was conducted to justify the proposed dissolution limit for all strengths.

Methods
This was a single-dose, two-way crossover study conducted in 22 healthy volunteers, comparing Ibuprofen, 200 mg, film-coated tablets (test batch with lowest observed dissolution rate) with Brufen, 200 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 12 hours post-dose. Plasma concentrations of ibuprofen were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2020-02-26 and 2020-03-18.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for ibuprofen, n=22.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**77.4583 ± 15.7780**	**21.1227 ± 4.5263**	**1.38 (0.75-4.02)**
Reference	**79.5622 ± 16.6601**	**21.9473 ± 5.9118**	**1.38 (0.75-5.00)**
***Ratio (90% CI)**	**97.60 (94.59-100.70)**	**97.83 (90.17-106.14)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell

within the conventional acceptance range of 80.00-125.00 %.

Discussion and overall conclusion
The pivotal bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and Ibuprofen oral use immediate release formulations 200-800 mg product-specific bioequivalence guidance (EMA/CHMP/356876/2017). The bioanalytical methods were adequately validated.

The study result from IBUPRL09206 can be extrapolated to the other strengths 200 mg, 400 mg and 600 mg, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of ibuprofen is linear between 200 mg and 800 mg. The study was performed with the highest strength in accordance with guideline recommendations.

Based on the submitted bioequivalence study, Ibuprofen is considered bioequivalent with Brufen.

The additional study (IBUPRL27419/2020-4819), using a test batch with lowest observed dissolution rate, was also performed in accordance with standards for bioequivalence testing and demonstrates bioequivalence compared to Brufen 200 mg. Although it is not optimal from a PK perspective that the study was performed with a lower strength, it is agreed that the study can be used to support the dissolution limit for all strengths. Thus, the suggested dissolution specification limit has been adequately justified.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary. Ibuprofen has been studied extensively in adults and children in a variety of painful and inflammatory conditions where its therapeutic effects are comparable to other NSAIDs. A number of large clinical trials have focused on the clinical uses, safety and pharmacological properties of ibuprofen given at prescription level doses (<2,400 mg/day using e.g. 600 mg and 800 mg tablets of ibuprofen) compared with other NSAIDs (including coxibs). In many of these studies, ibuprofen was used as a reference drug.

IV.3 Risk Management Plan

The MAH has submitted an updated risk management plan (version 0.2, signed 04 August 2020), 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 Ibetin, 200 mg, 400 mg, film-coated tablet.

Since this type of application (article 10 (1) generic) has no PSUR requirements, the applicant has agreed with comments from CMS CZ to delete such statements in the RMP. The applicant is committed to provide a final updated version of the RMP by EoP.

Safety specification

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 0.2 signed 04 August 2020 is considered acceptable. It is in line with the RMP of the reference product.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Ibuprofen Zentiva, SE/H/2058/01-03/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products, Ibetin are found adequate. There are no objections to approval of Ibetin from a non-clinical and clinical point of view. The submitted bioequivalence data show that bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment
N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Ibetin, 200 mg, 400 mg, film-coated tablet was positively finalised on 2021-02-24.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se