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Decentralised Procedure

Public Assessment report

Scientific discussion

IBUSTAD 200
IBUSTAD 400
ibuprofen

SK/H/0327/001-002/DC

Date of this report: October 2025

This module reflects the scientific discussion for the approval of IBUSTAD. The procedure was finalised at D210 (09 July 2025). For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States have agreed to grant a marketing authorisation for IBUSTAD 200 and IBUSTAD 400.
IBUSTAD 200 is indicated in adults and children weighing more than 20 kg (approximately 6 years and older) for the short-term treatment of fever and/or pain such as headaches, flu-like symptoms, dental pain, aches and pains and painful periods.

IBUSTAD 400 is indicated in adults and adolescents weighing more than 40 kg (approximately 12 years and older) for symptomatic treatment of pain and inflammation in arthritic diseases (e.g. rheumatoid arthritis), degenerative arthritic conditions (e.g. osteoarthritis), and in painful swelling and inflammation after soft tissue injuries.

Symptomatic treatment of:
- mild to moderate pain
- fever

A comprehensive description of the indications and posology is given in the SmPC.

II EXECUTIVE SUMMARY

II.1 Problem statement

Not applicable.

II.2 About the product

Mechanism of action
Ibuprofen is an analgesic, antipyretic, and anti-inflammatory medication. The principal mechanism of action of ibuprofen and other NSAIDs is inhibition of prostaglandin biosynthesis. Prostaglandins contribute to fever, pain, and inflammation by sensitizing tissues to pain- and inflammation-producing mediators such as histamine, 5-hydroxytryptamine, and kinins. The committed step in prostaglandin biosynthesis is catalysed by prostaglandin endoperoxide synthase, also known as cyclooxygenase. NSAIDs decrease prostaglandin biosynthesis by inhibiting cyclooxygenase.

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivatives.
ATC code: M01AE01

II.3 General comments on the submitted dossier

This was an application for a marketing authorisation (MAA) of a medicinal product for human use as it is defined in Article 10(1) (generic application) of the European Directive 2001/83/EC as amended. Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovak Republic acting as RMS. The Applicant Drehm Pharma GmbH submitted this MAA under procedural number SK/H/0327/001-002/DC; CMS was France.

As a reference medicinal product for the purposes of establishing the expiry of the data protection period Brufen 200 mg filmdragerade tabletter from Viatris AB, Sweden was chosen.
A European Reference Product was used in both RMS and CMS for the 200 mg strength: Brufen 200 mg filmdragerade tabletter, Viatris AB, authorised in Sweden.

Reference medicinal product used in RMS for the 400 mg strength: Brufen 400 mg filmom obalené tablety, Viatris Healthcare Limited, authorised in Slovakia.
Reference medicinal product used in CMS for the 400 mg strength: BRUFEN 400 mg comprimé pelliculé, Viatris Medical, authorised in France.

For the demonstration of a bioequivalence Brufen 600 mg compresse rivestite from Mylan Italia, Italy was chosen.

Assessment of similarity with authorised orphan medicinal product(s) under market exclusivity

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

GCP aspects

A statement on the application of appropriate GCP standards in the submitted bioequivalence study no. 20-VIN-0437 has been provided.

GMP aspects

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

The finished product is presented as a film-coated tablet, containing 200 mg or 400 mg of ibuprofen as an active substance.

IBUSTAD 200 mg film-coated tablets are white to off white, round shaped, film-coated tablets with 'G2' debossing on one side and plain on other side. Approximately, the tablet diameter is 9 mm and tablet thickness is 5 mm.

IBUSTAD 400 mg film-coated tablets are white to off white, oval shaped, film-coated tablets with 'I 6' debossing on one side and plain on other side. Approximately, the tablet dimensions are 14 mm x 8 mm and tablet thickness is 6 mm.

Medicinal product is packed in clear, transparent PVC/Aluminium blister packs in an outer carton box containing 10 tablets per blister or unit dose blister.

Available in pack sizes of:
200 mg: 20, 30, 50, 100 and 20x1, 30x1, 50x1, 100x1 tablets
400 mg: 20, 30 and 20x1, 30x1, 50x1, 100x1 tablets

The other ingredients are:

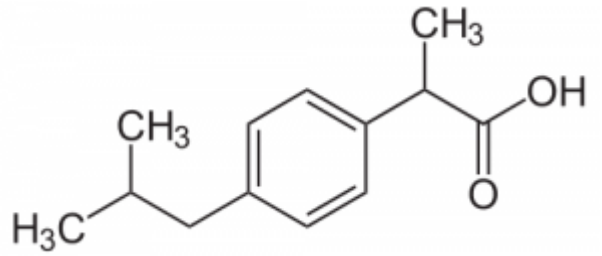
Tablet core
Cellulose, microcrystalline (E460)
Starch, pregelatinised (prepared from maize starch)
Povidone
Sodium laurilsulfate (E487)
Croscarmellose sodium (E468)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E572)

Film-coating
Titanium dioxide (E 171)
Hypromellose 2910 (E464)
Hydroxypropyl Cellulose (E463)
Macrogol (E1521)

Drug substance

INN	Ibuprofen
Chemical names	p-isobutyl Hydra tropic acid, p-isobutylphenyl propionic acid 4-isobutyl-alpha-methylphenylacetic acid "(2RS)-2-(4-Isobutylphenyl) propanoic acid"

Molecular structure



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.

The active substance ibuprofen is described in the European Pharmacopoeia monograph No. 0721. Information on the manufacturing process and process controls has been supplied to, and approved by, the European Directorate for the Quality of Medicines (EDQM) in relation to the Certificate of Suitability Procedures (CEP) for ibuprofen (Ph. Eur.).

The specification from the drug product manufacturer was provided and it includes test methods in

accordance with the Ph.Eur. monograph for ibuprofen and additional tests for residual solvents (CEP), particle size, identification by FT-NIR and assay by titrimetry. All analytical methods are suitable for the intended purpose. Batch data by drug substance manufacturer and drug product manufacturer provided comply with the active pharmaceutical ingredient (API) specification.

Drug product

The drug product is a film-coated tablet in 200 mg and 400 mg strengths.
Description of the drug product of each strength was provided. Two strengths are weight proportional and quantitatively proportional.
Finished drug product was developed as a generic product to Brufen 600 mg procured from Mylan Italia. The quantitative and qualitative composition of excipients slightly differ. The choice of excipients was justified and their functions explained. All excipients in the drug product formulation are well-known and of pharmacopeial quality. The composition of coating has been provided.

The proposed drug product is manufactured by a pharmaceutically standard process. Manufacturing process uses wet granulation, involving several steps as sifting, dry mixing, granulation, milling, drying, blending and compression followed by film-coating stage and packaging of the drug product.
The in-process controls for various manufacturing stages (blending, compression, coating) were described.

The finished product release and shelf-life specifications include appropriate tests and limits for appearance (in-house), identification (chemical, HPLC; in-house), average weight (in-house), dimensions (in-house), thickness (in-house), water content by Karl-Fisher (in-house), dissolution (UV; in-house), uniformity of dosage units (Ph.Eur.), assay (HPLC; in-house), related substances (HPLC; in-house), and microbiological quality (Ph.Eur.). The proposed specification (release, shelf-life) for the drug product is in line with ICH Q6A and it is acceptable for this type of dosage form.

Batch analytical data of three consecutive exhibit validation batches of both strengths (200 mg and 400 mg) have been provided. All results are within the predefined acceptance criteria.
A risk assessment report for formation of nitrosamines was provided, and no risk of nitrosamine presence was identified in the proposed drug product.

The proposed primary packaging of the drug product is PVC/Aluminium blister foil.

A shelf-life of 36 months was proposed for the drug product, and it was based on acceptable 6 months accelerated and 36 months long-term stability results. No special storage conditions are required.

III.2 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 were not required. Overview based on literature review was, thus, appropriate.

All excipients are well established. There were no raised non-clinical issues regarding impurities.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology was adequate. The non-clinical section of the SmPC was acceptable and in accordance with the reference medicinal product information.

Environmental Risk Assessment (ERA)

Since IBUSTAD is intended for generic substitution, this should not lead to an increased exposure to the environment. A complete environmental risk assessment was therefore not deemed necessary.

Consumption data from France and Slovakia from past years did not show increasing trend of ibuprofen usage. Thus, an increase in risk to the environment is not expected.
Ibuprofen's characteristics (high lipophilicity and low biodegradation) favour its bioaccumulation in the environment, and its biological activity suggests that it is harmful to several aquatic species. The environmental accumulation of pharmaceutical compounds with a biological action such as ibuprofen's could increase their toxicity in aquatic organisms. Given the facts which indicate that ibuprofen has the potential to pose a risk to aquatic environment, the following statements were included in sections 5.3 and 6.6 of the SmPC:

SmPC 5.3:
Published data have shown that ibuprofen may pose a risk for the aquatic environment (see section 6.6).

SmPC 6.6:
This medicinal product may pose a risk to the environment (see section 5.3).

III.3 Clinical aspects

The clinical overview based on the scientific literature on the clinical pharmacology, efficacy and safety was adequate. No further clinical studies were required, besides one bioequivalence study, which is discussed below.

Bioequivalence study no. 20-VIN-0437

To support the application, the applicant has submitted one bioequivalence study no. 20-VIN-0437. Purpose and methodology of the study was to assess the bioequivalence of a generic ibuprofen 600 mg film-coated tablets to the reference medicinal product, Brufen 600 mg (by Mylan Italia, Italy). A single-dose, randomised, two-period, two-sequence crossover design was used, with fasting conditions for all participants.

Study design
The study, conducted on 32 healthy adult male subjects, employed a five-day washout period between treatments. Blood samples were collected at 24 intervals over 12 hours to cover the drug's absorption and elimination phases.

Fasting conditions: The study adhered to fasting conditions to prevent food-induced absorption variability, which is standard practice for ibuprofen bioequivalence studies.

Compliance with standards: The study followed good clinical practice (GCP) and good laboratory practice (GLP) standards. Ethical guidelines, including the Declaration of Helsinki and ICH-GCP, were strictly followed, ensuring study reliability and participant safety.

Analytical methodology: Plasma levels of ibuprofen were measured using a validated LC-MS/MS method, ensuring high sensitivity, specificity, and accurate quantification of ibuprofen.

Pharmacokinetic parameters: Key pharmacokinetic measures, including C_{max}, AUC0-t, and AUC0-∞, were used to determine the rate and extent of absorption, while Tmax and other secondary parameters offered additional insights into the drug's pharmacokinetic profile.

Statistical analysis: Log-transformed data were analyzed using ANOVA, with Cmax and AUC ratios tested against the bioequivalence range of 80.00%–125.00%, which the study's results met satisfactorily.

Subject participation: Of 32 enrolled, 29 subjects completed the study, and these participants were included in the final pharmacokinetic and statistical analysis.

Results

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, Tmax median, range)

Pharmacokinetic Parameters (Units)	Arithmetic Mean ± SD (%CV) (N =29)	
	Reference Product (R)	Test Product (T)
C_{max} (ug/mL)	42.887 ± 7.6435 (17.82%)	43.022 ± 6.1799 (14.36%)
#T_{max} (hr)	1.250 (0.50 - 4.50)	1.500 (0.67 - 4.50)
AUC_{0-t} (hr*ug/mL)	141.909 ± 28.0195 (19.74%)	143.322 ± 28.5882 (19.95%)
$AUC_{0-\infty}$ (hr*ug/mL)	144.658 ± 28.8584 (19.95%)	145.977 ± 29.3696 (20.12%)
$t_{½}$ (hr)	1.891 ± 0.2891 (15.29%)	1.878 ± 0.3268 (17.40%)
λz (1/hr)	0.376 ± 0.0644 (17.12%)	0.379 ± 0.0631 (16.64%)
AUC_%Extrap_obs (%)	1.860 ± 0.7003 (37.66%)	1.791 ± 0.8134 (45.43%)

#For T_{max} median (min – max)

Table 2: Pharmacokinetic parameters expressed as geometric LS means, its ratio and 90% Confidence Interval

PK Parameters (Unit)	Geometric Least Square Means and Its Ratio (N = 29)			Intra subject %CV	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) (%)			
C_{max} (ug/mL)	42.904	42.406	101.17	12.80	95.54% - 107.15%	100.00
AUC_{0-t} (hr*ug/mL)	141.372	139.567	101.29	7.90	97.76% - 104.95%	100.00

Table 3: Additional pharmacokinetic data for the bioequivalence study no. 20-VIN-0437

Plasma concentration curves where	**Related information**
- $AUC_{(0-t)}/AUC_{(0-\infty)}<0.8$[1]	NA
- Cmax is the first point	NA
- Pre-dose sample > 5% Cmax	NA

Conclusion

Both Cmax and AUC parameters for the test product fell within the acceptable range, confirming bioequivalence of ibuprofen 600 mg with the reference medicinal product Brufen 600 mg from Mylan Italia, Italy.

Biowaiver

The applicant sought the biowaiver for lower strengths, i.e. 200 mg and 400 mg based on the bioequivalence study data for ibuprofen 600 mg film-coated tablets.
Considering the data obtained from the bioequivalence study conducted with 600 mg strength and comparative dissolution profiles performed with the two lower strengths, the biowaiver for conducting studies was proposed based on the following criteria:

1. All three strengths (200 mg, 400 mg, 600 mg) are manufactured by the same manufacturing process at the same manufacturing site.

2. The qualitative composition of these three strengths (200 mg, 400 mg, 600 mg) is the same.

3. The composition of these strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all three strengths.

4. The pharmacokinetics of ibuprofen is linear over the therapeutic range i.e. 200 mg to 600 mg.

5. The comparative dissolution profile data confirmed that two lower strengths (i.e. ibuprofen 200 mg & ibuprofen 400 mg) have dissolution profiles comparable to higher strength, i.e. ibuprofen 600 mg film-coated tablets on which the bioequivalence study was conducted.

Based on applicant´s claims that were supported by submitted data, biowaiver was granted for both lower strengths, i.e. 200 mg and 400 mg.

Summary Pharmacovigilance system

The Applicant has submitted a signed Summary of Applicant´s Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considered the Summary acceptable.

Risk Management Plan

The Applicant 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 IBUSTAD.

Safety specification
Table 4: Summary of safety concerns

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 were proposed by the applicant, which was endorsed.

Risk minimisation measures
The safety information in the proposed product information is aligned to the safety concerns for ibuprofen published on the CMDh website resulting from the HaRP Assessment Report. No additional risk minimisation activities are proposed by the applicant, which was endorsed.

Summary of the RMP

The submitted Risk Management Plan was considered acceptable.

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.

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 BENEFIT RISK ASSESSMENT

Non-clinical
Non-clinical overview based on literature review was appropriate. All excipients are well established. No non-clinical issues regarding impurities were raised.
Given the facts which indicate that ibuprofen has the potential to pose a risk to aquatic environment, the respective statements were included in sections 5.3 and 6.6 of the SmPC.

Clinical
Based on the results of submitted bioequivalence study it was concluded that ibuprofen 600 mg is bioequivalent with the reference medicinal product Brufen 600 mg from Mylan Italia, Italy. Biowaiver for lower strengths 200 mg and 400 mg was accepted.

Quality
Quality aspects of the dossier were adequately described; specifications of ibuprofen were in line with monograph no. 0721 published under Ph. Eur., and that of finished medicinal product are adequately controlled based on approved specification.

VI RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

VI.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

None

VI.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

None

VI.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

VI.4 Package Leaflet (PL)

VI.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

VI.4.2 Assessment of User Testing

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.5 Labelling

The approved Labelling is available in the MRI Product Index.