LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ibuprofen NET
(ibuprofen)

5.4.1-2024-041411

This module reflects the scientific discussion for the approval of Ibuprofen NET. The procedure was finalised at 2024-05-16. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Ibuprofen NET, 400 mg, Film-coated tablet.

The active substance is ibuprofen. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Ibuprofen is a racemic propionic acid derivative belonging to anti-inflammatory and antirheumatic products, non-steroids (ATC code: M01AE01).

It reduces pain and fever by reversible inhibition of cyclo-oxygenase COX-1 and COX-2 enzymes to decrease the conversion of arachidonic acid into PG endoperoxides including thromboxane and prostacyclin (PGI2). Ibuprofen is used to treat mild to moderate pain and fever associated with common cold, musculoskeletal pain, common headache, migraine, rheumatic pain, dysmenorrhoea, and dental pain.

The proposed indications for the current product:

Akuta smärttillstånd av lätt till måttlig intensitet. Feber hos vuxna och ungdomar. Dysmenorré utan organisk orsak. Artros, reumatoid artrit.

II.2 General comments on the submitted dossier

The application for Ibuprofen NET, 400 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Brufen, film-coated tablet, 400 mg authorised in SE since 1975, with Viatris AB as marketing authorisation holder.

The reference products used in the bioequivalence studies are Brufen, 200 mg, film-coated tablet and Brufen, 600 mg, film-coated tablet from Sweden with Viatris AB as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The MPA 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 European Community, the MPA 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.

For manufacturing sites outside the European Community, the MPA has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of

information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

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

GCP aspects
A statement on the application of appropriate GCP standards in the submitted studies has been provided. Study ARL/13/497: The clinical and the bioanalytical facilities were inspected by the UK authority in 2015, without any critical findings. Study 17-VIN-0418: The clinical and the bioanalytical facilities were inspected by the UK authority in 2016, without any critical findings. No issues regarding GCP have been identified. No inspection of the submitted bioequivalence studies is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are well known. As ibuprofen is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Ibuprofen NET is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Ibuprofen NET from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Ibuprofen NET (Ibuprofen) with the reference product Brufen.

Pharmacokinetic properties of the active substance
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, but food does not markedly affect total bioavailability. The SmPC for the originator states that in order to achieve a faster onset of action, the dose may be taken on an empty stomach, but it is recommended that patients with sensitive stomachs take ibuprofen with food. Thus, no firm guidance is given regarding concomitant food intake in the SmPC of the originator. Ibuprofen is generally used as the racemic mixture of the two enantiomers, S(+)-ibuprofen and R(-)-ibuprofen, although S-ibuprofen (dexibuprofen) is available in some countries. There are several differences in the metabolism and pharmacokinetic properties of the two enantiomers. Approximately 40-60% of the R-ibuprofen is inverted *in vivo* to the pharmacologically active S-ibuprofen and there is no detectable inversion in the opposite direction. Ibuprofen has a non-linear relationship between AUC and dose at high doses, with a smaller than expected increase in AUC with increasing dose. This non-linearity has been attributed to non-linear plasma protein binding since free ibuprofen plasma AUC was linearly related to the dose. It has however been demonstrated that there were no significant changes in dose-normalised AUC of the active S-enantiomer in the dose range 200-600 mg. A review article (Rainsford 2009) concludes that the pharmacokinetics of ibuprofen is approximately linear up to 1200 mg. The plasma elimination half-life is approximately 2 hours.

Study ARL/13/497 (200 mg)
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Ibuprofen, 200 mg, tablets with Brufen, 200 mg, tablets under fasting conditions. The study was conducted at Accutest Research Laboratories Pvt. Ltd., Khairane, Navi Mumbai, India between 4th and 16th July 2014. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of S(+)-ibuprofen and R(-)-ibuprofen were determined with an adequately validated LC-MS/MS method.

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for S(+)-ibuprofen, n=27.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**37.03±10.62**	**9.39±2.44**	**1.25 (0.83-4.00)**
Reference	**35.61±9.49**	**8.85±2.16**	**2.00 (0.66-4.00)**
***Ratio (90% CI)**	**103.27 (99.83-106.83)**	**105.82 (98.13-114.11)**	**-**
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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for R(-)-ibuprofen, n=27.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**25.88±5.62**	**8.93±2.46**	**1.25 (0.50-4.00)**
Reference	**25.46±5.94**	**8.39±2.05**	**2.00 (0.50-4.00)**
***Ratio (90% CI)**	**101.69 (97.29-106.28)**	**105.55 (96.56-115.37)**	**-**
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% for both enantiomers.

However, the t_{max} results do not fulfil the bioequivalence assessment criteria in the product-specific bioequivalence guidance for ibuprofen. The difference in median t_{max} between the test and reference products was more than 20%. However, the applied strength is 400 mg and a higher strength, 600 mg (not applied for) has been studied which is in accordance with guideline recommendations and the product-specific bioequivalence guidance for ibuprofen. Study ARL/13/497 with the 200 mg strength is included for completeness but the bioequivalence assessment is based on Study 17-VIN-0418 with the higher strength.

Study 17-VIN-0418 (600 mg)
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Ibuprofen, 600 mg, film-coated tablets with Brufen, 600 mg, film-coated tablets under fasting conditions. The study was conducted at Veeda Clinical Research Pvt. Ltd, Vejalpur, Gujarat, India between 2nd and 13th April 2018. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of S(+)-ibuprofen and R(-)-ibuprofen were determined with an adequately validated LC-MS/MS method.

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

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for S(+)-ibuprofen, n=33.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**96.30±32.25**	**23.83±4.65**	**2.00 (0.83-3.50**
Reference	**95.87±37.79**	**23.60±5.65**	**2.00 (0.67-6.00)**
***Ratio (90% CI)**	**101.74 (98.72-104.85)**	**102.42 (96.51-108.68)**	**-**
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*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for R(-)-ibuprofen, n=33.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**63.24±19.09**	**21.22±4.87**	**1.75 (0.50-3.50)**
Reference	**61.07±19.28**	**20.33±5.57**	**1.75 (0.67-4.00)**
***Ratio (90% CI)**	**103.68 (96.38-111.53)**	**105.73 (97.57-114.58)**	**-**
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% for both enantiomers. The t_{max} results fulfil the bioequivalence assessment criteria in the product-specific bioequivalence guidance for ibuprofen. The median t_{max} was comparable (≤ 20% difference) between the test and reference products. Data for R-ibuprofen were submitted as supportive data.

A biowaiver was sought for the applied strength of 400 mg.

Discussion and overall conclusion
Bioequivalence studies have been submitted for the 200 mg and 600 mg strengths (not applied for). The bioequivalence studies and the 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 the Ibuprofen product-specific guidance (EMA/CHMP/356876/2017 Rev.1*). The bioanalytical methods were adequately validated.

A higher strength, 600 mg (not applied for) has been studied which is in accordance with guideline recommendations and the product-specific bioequivalence guidance for ibuprofen. Study ARL/13/497 with the 200 mg strength is included for completeness but the bioequivalence assessment is based on Study 17-VIN-0418 with the higher 600 mg strength.

Based on the submitted bioequivalence study 17-VIN-0418, Ibukron 600 mg tablets are considered bioequivalent with Brufen 600 mg tablets.

Absence of studies with the applied strength of 400 mg is acceptable, as all conditions for biowaiver for additional strength(s), 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.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH: Evolan Pharma AB
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH'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 MPA considers the Summary acceptable.

Risk Management Plan
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 Ibuprofen NET.

Part II Safety specification
The MAH has submitted the version 0.1 RMP dated 20-Jan-2025 and proposed the following safety concerns:

Summary of safety concerns	
Important identified risk	None
Important potential risks	None
Missing information	None

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

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 20-Jan-2025 is 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)

Active substance is currently listed in the published EURD list

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.

Renewal date
The renewal date will be 5 years after approval date.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Ibuprofen NET, is found adequate. There are no objections to approval of Ibuprofen NET, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

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

Post approval commitments
N/A

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

- **Additional risk minimisation measures (including educational material)**

  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available on the Swedish MPA website.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available on the Swedish MPA website.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Ibuprofen NET 400 mg (5.4.1-2018-61977) for content and to Kalcium/Kolekalciferol Evolan film-coated tablets (5.4.1-2020-32064) for layout.

The proposed bridging regarding content and layout is considered acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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