LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Ibuprofen Evolan
(ibuprofen)

2016-2026 - 2027

This module reflects the scientific discussion for the approval of Ibuprofen Evolan. The procedure was finalised on 2019-01-30. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Ibuprofen Evolan, 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, Evolan Pharma AB 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, 200 mg and 400 mg, film-coated tablet authorised in SE since 1975, with BGP Products AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Brufen, 200 mg, film-coated tablet from SE with BGP Products AB (Abbot at the time of study) as marketing authorisation holder.

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 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

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 recent 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

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. 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 S-(+) ibuprofen and R-(-) ibuprofen.

Table 1. 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*

Table 2. 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*

As discussed above, the linearity of ibuprofen is a complex issue. However, regarding biowaiver for additional strengths the relevant issue is whether the difference in dose-adjusted AUC is no more than 25 % when comparing the studied strength and the strength for which a waiver is sought. It has been concluded in several procedures during the last years that according to the definition in the current bioequivalence guideline the pharmacokinetics of ibuprofen can be considered to be linear in the interval 200-600 mg. Thus, it is concluded that in the interval relevant for strength biowaiver, 200-400 mg, ibuprofen can be considered to have linear pharmacokinetics. For drugs with linear pharmacokinetics, bioequivalence studies should in general be conducted at the highest strength, unless the drug substance is highly soluble or if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. Ibuprofen is not a high solubility drug and can be administered to healthy volunteers. Therefore, from a pharmacokinetic perspective a biowaiver for the highest strength of 400 mg was questioned in the primary round. In the recently adopted product-specific guidance document for ibuprofen, it is concluded that pharmacokinetics of ibuprofen is linear in the range 200-800 mg and that the study should be performed with the highest applied strength.

In response, the applicant submitted a bioequivalence study with a higher strength (600 mg), currently not applied for. From a pharmacokinetic perspective, this is acceptable since ibuprofen has linear pharmacokinetics in the dose range 200-600 mg and considering that it is not a highly soluble drug.

Study 17-VIN-0418

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. 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 S-(+) ibuprofen and R-(-) ibuprofen. Data for R-ibuprofen were submitted as supportive data.

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 (96.57-114.58)**	**103.68 (96.38-111.53)**	**-**
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*

Based on the submitted bioequivalence studies, Ibuprofen 200 mg tablets are considered bioequivalent with Brufen 200 mg tablets and Ibuprofen 600 mg tablets (not applied for in this application) are considered bioequivalent with Brufen 600 mg tablets. The results of study 17-VIN-0418 with 600 mg formulation CAN be extrapolated to the other strength 400 mg, according to conditions in the Guideline on the investigation of Bioequivalence; CHMP/QWP/EWP/1401/98 Rev. 1, section 4.1.6. Thus, bioequivalence between test and reference product has been adequately demonstrated.

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.

IV.3 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 Evolan, 200 mg and 400 mg, film-coated tablet.

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	□ Gastrointestinal bleeding, ulceration and perforation □ Cardiovascular effects (arterial thrombotic events) □ Severe cutaneous skin reactions (e.g. Steven Johnson Syndrome, Toxic Epidermal Necrolysis) □ Use in pregnancy
Important potential risks	□ None
Missing information	□ None

Summary table of safety concerns as approved in RMP

Important identified risks	
Important potential risks	
Missing information	

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 RMP is approved.

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 Apofri, 200 and 400 mg, filmcoated tablets, approved in the national procedure (111:2007/37918). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Ibuprofen Evolan is found adequate. There are no objections to approval of Ibuprofen Evolan, 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 application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 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

Ibuprofen Evolan, 200 mg and 400 mg, film-coated tablets was approved in the national procedure on 2019-01-30.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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