Public Assessment Report

Decentralised Procedure

IBUPROFEN LYSINE 342 MG FILM-COATED TABLETS
(Ibuprofen Lysine)

Procedure No: UK/H/5322/001/DC

UK Licence No: PL 40168/0003

INN-FARM d.o.o.
LAY SUMMARY

Ibuprofen Lysine 342 Film-coated Tablets
(Ibuprofen Lysine)

This is a summary of the public assessment report (PAR) for Ibuprofen Lysine 342 mg Film-coated Tablets (PL 40168/0003). It explains how Ibuprofen Lysine 342 mg Film-coated Tablets were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Ibuprofen Lysine 342 mg Film-coated Tablets.

For practical information about Ibuprofen Lysine 342 mg Film-coated Tablets, patients should read the Patient Information Leaflet or contact their doctor or pharmacist.

What are Ibuprofen Lysine 342 mg Film-coated Tablets and what are they used for?

Ibuprofen Lysine 342 mg Film-coated Tablets are a ‘generic medicine’. This means that Ibuprofen Lysine 342 mg Film-coated Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Nurofen Migraine Pain (Reckitt Benckiser Healthcare (UK) Limited).

Ibuprofen Lysine 342 mg Film-coated Tablets are used to help provide relief from symptoms of mild to moderate pain, such as headache, dental pain, period pain, and or fever and pain associated with the common cold.

How do Ibuprofen Lysine 342 mg Film-coated Tablets work?

Ibuprofen Lysine 342 mg Film-coated Tablets contain the active ingredient ibuprofen lysine which is a lysine salt of ibuprofen. This medicine belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs) which relieve pain and lower temperature in a fever.

How are Ibuprofen Lysine 342 mg Film-coated Tablets used?

This medicine can be obtained without a prescription. Ibuprofen Lysine 342 mg Film-coated Tablets are for short term use only. Adults and adolescents weighing from 40 kg are advised to take one or two tablets with water, up to three times a day as required. It is recommended to leave at least 6 hours between doses and it is also advised not to take more than six tablets in any 24 hour period.

This medicine is not recommended for children under the age of 12 or adolescents weighing less than 40 kg.

Please read Section 3 of the Patient Information Leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

What benefits of Ibuprofen Lysine 342 mg Film-coated Tablets have been shown in studies?

Ibuprofen Lysine 342 mg Film-coated Tablets are a generic medicine; therefore, studies in patients have been limited to tests to determine that this medicine is bioequivalent to the reference medicine, Nurofen Migraine Pain. Two medicines are bioequivalent when they produce the same levels of the active ingredient in the body.

What are the possible side effects of Ibuprofen Lysine 342 mg Film-coated Tablets?

Because Ibuprofen Lysine 342 mg Film-coated Tablets are a generic medicine and is considered to be bioequivalent to the reference medicine, Nurofen Migraine Pain, its benefits and possible side effects are
taken as being the same as the reference medicine.

For the full list of restrictions, see the Patient Information Leaflet.

**Why are Ibuprofen Lysine 342 mg Film-coated Tablets approved?**

It was concluded that, in accordance with EU requirements, Ibuprofen Lysine 342 mg Film-coated Tablets have been shown to have comparable quality and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as Nurofen Migraine Pain, the benefits are greater than its risk and recommended that it can be approved to provide relief from symptoms of mild to moderate pain, such as headaches, period pains, dental pain, and fever and pain associated with the common cold.

**What measures are being taken to ensure the safe and effective use of Ibuprofen Lysine 342 mg Film-coated Tablets?**

A risk management plan has been developed to ensure that Ibuprofen Lysine 342 mg Film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the Patient Information Leaflet for Ibuprofen Lysine 342 mg Film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be reviewed continuously.

**Other information about Ibuprofen Lysine 342 mg Film-coated Tablets**

The Czech Republic, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Slovenia, Slovakia, Spain and the United Kingdom agreed to grant a Marketing Authorisation for Ibuprofen Lysine 342 Film-coated Tablets on 06 July 2014. A Marketing Authorisation was granted in the UK on 29 July 2014.

The full initial PAR and the subsequent variation to amend the legal status to Pharmacy only (P) for Ibuprofen Lysine 342 mg Film-coated Tablets follows this summary. Suitable labelling has been provided. For more information about treatment with Ibuprofen Lysine 342 mg Film-coated Tablets, read the Patient Information Leaflet or contact your doctor or pharmacist.

This summary was last updated in February 2015.
TABLE OF CONTENTS

Module 1: Information about initial procedure  
Module 2: Summary of Product Characteristics  
Module 3: Patient Information Leaflet  
Module 4: Labelling  
Module 5: Scientific discussion during initial procedure  
Module 6: Steps taken after initial procedure  

I Introduction
II About the product
III Scientific overview and discussion
   III.1 Quality aspects
   III.2 Non-clinical aspects
   III.3 Clinical aspects
IV Overall conclusion and benefit-risk assessment
Module 1
Information about initial procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Ibuprofen Lysine 342 mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td>Active Substances</td>
<td>Ibuprofen lysine</td>
</tr>
<tr>
<td>Form</td>
<td>Tablets</td>
</tr>
<tr>
<td>Strength</td>
<td>342 mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>INN-FARM d.o.o. Maleševa ulica 014 1000 Ljubljana Slovenia</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>The Czech Republic, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Slovenia, Slovakia, Spain</td>
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<td>Procedure Number</td>
<td>UK/H/5322/001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210 – 06 July 2014</td>
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</tbody>
</table>
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summary of Product Characteristics (SmPC) for products that have been granted Marketing Authorisations at a national level is available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflet for products that are granted Marketing Authorisations at a national level is available on the MHRA website.
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that this application for Ibuprofen Lysine 342 mg Film-coated Tablets (PL 40168/0003; UK/H/5322/001/DC) could be approved. This application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and the Czech Republic, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Slovenia, Slovakia and Spain as Concerned Member States (CMS).

This application was made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the reference product, Nurofen Migraine Pain. Nurofen Migraine Pain was originally granted a marketing authorisation to Crookes Healthcare Limited on 27 July 2000 with the product name Crookes Analgesic Tablets (PL 00327/0125). By way of variation the product name was amended to Nurofen Migraine Pain on 20 September 2002. Following a change of ownership, the Marketing Authorisation was transferred to the current Marketing Authorisation Holder; Reckitt Benckiser Healthcare (UK) Limited (PL 00063/0380) on 29 April 2011.

This product can be obtained without a prescription from a pharmacy (legal classification P).

Ibuprofen Lysine 342 mg Film-coated Tablets are indicated in adults and adolescents, weighing from 40 kg body weight (12 years of age and above), for the symptomatic treatment of mild to moderate pain, such a headache, period pain, dental pain, and fever and pain associated with the common cold.

Ibuprofen Lysine 342 mg Film-coated Tablets contain the active substance ibuprofen lysine. Ibuprofen Lysine 342 mg Film-coated Tablets are a non-steroidal anti-inflammatory drug (NSAID) that in the conventional animal-experiment inflammation models has proven to be effective via prostaglandin-synthesis inhibition. In humans, ibuprofen reduces inflammatory-related pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation. Following oral administration, ibuprofen lysine dissociates to ibuprofen acid and lysine. Lysine has no recognised pharmacological activity. The pharmacological properties of ibuprofen lysine, therefore, are the same as those of ibuprofen acid.

No new non-clinical studies were conducted, which is acceptable given that this application was based on being a generic medicinal product of the reference product, which has been licensed for over 10 years.

With the exception of the bioequivalence study comparing the pharmacokinetic profile of the applicant’s test product Ibuprofen Lysine 342 mg Film-coated Tablets to that of the reference product, Nurofen Migraine Pain (which contains 342 mg ibuprofen lysine) no new clinical studies were conducted. This is acceptable given that this application was based on being a generic medicinal product of the reference product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured 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 this product.

The RMS and CMS considered that the application could be approved at the end of procedure on 06 July 2014. After a subsequent national phase, a marketing authorisation was granted in the UK on 29 July 2014.
II ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Ibuprofen Lysine 342 mg Film-coated Tablets |
| Name(s) of the active substance(s) (INN) | Ibuprofen lysine |
| Pharmacotherapeutic classification (ATC code) | Anti-inflammatory and anti-rheumatic products, Non-Steroids, Propionic acid derivates (M01AE01) |
| Pharmaceutical form and strength(s) | Tablets 342 mg |
| Reference numbers for the Decentralised Procedure | UK/H/5322/001/DC |
| Reference Member State | UK |
| Member States concerned | The Czech Republic, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Slovenia, Slovakia, Spain |
| Marketing Authorisation Number(s) | PL 40168/0003 |
| Name and address of the authorisation holder | INN-FARM d.o.o. Maleševa ulica 014 1000 Ljubljana Slovenia |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance – **Ibuprofen lysine**

rINN: Ibuprofen lysine

Chemical name:

(2RS)-2-[4-(2-methylpropyl)phenyl]propanoic acid compound with (2R,S)-2,6-diamino-hexanoic acid Lysine, mono[a-methyl-4-(2-methylpropyl)benzeneacetate]

2-(4-Isobutyl-phenyl)-propionic acid; compound with 2,6-diamino-hexanoic acid

α-methyl-4-(2-methylpropyl)-benzene-acetic acid, 2,6-diamino-hexanoic acid salt

Lysine salt of 2(4-isobutylphenyl) propionic acid

Structure:

![Structure of Ibuprofen Lysine]

Molecular formula: $C_{19}H_{32}N_{2}O_{4}$

Molecular weight: $352.48$ g/mol

Appearance: white crystalline powder.

Solubility: It is freely soluble in water, sparingly soluble in methanol and practically insoluble in acetone, ether, dichloromethane chloride, and ethyl acetate.

Synthesis of the active substance from the designated starting material has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data has been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

Appropriate specifications are provided for the active substance ibuprofen lysine, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided that comply with the proposed specifications.

Suitable Certificates of Analysis have been provided for all reference standards used. Satisfactory specifications have been provided for all packaging used for storing the active substance, ibuprofen lysine. The primary packaging has been shown to comply with current legislation concerning materials in contact with foodstuff.
**P. Medicinal Product**

**Other Ingredients**

Other ingredients consist of the following pharmaceutical excipients:

Tablet core:
Silicified microcrystalline cellulose which consists of; cellulose, microcrystalline and silica, colloidal anhydrous, copovidone, croscarmellose sodium (E468), silica colloidal anhydrous, magnesium stearate (E470b), talc (E553b).

Film Coat:
Opadry II pink 57U34579 which consists of; hypromellose (E464), titanium dioxide (E171), polydextrose, talc (E553b), maltodextrin, medium chain triglycerides, ponceau 4R aluminium lake (E124), sunset yellow aluminum lake (E110), indigo carmine aluminium lake (E132).

Opadry fx silver 62W28547 which consists of; carmellose sodium (E466), maltodextrin, glucose monohydrate, mica-based pearlescent pigment (Mica/Titanium dioxide) (E555/E171), soya lecithin (E322).

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of silicified microcrystalline cellulose and polydextrose which comply with the national formulary. The individual constituents of silicified microcrystalline cellulose all comply with relevant European Pharmacopoeia monographs. Opadry II pink 57U34579 and Opadry fx silver 62W28547 both comply with in-house specifications, whilst the individual constituents of Opadry II pink 57U34579 and Opadry fx silver 62W28547 (with the exception of polydextrose) all comply with the European Pharmacopoeia monographs. All colouring agents used have been shown to comply with EU Directive 95/45/EC, concerning the use of colours in foodstuff.

None of the excipients are of animal or human origin. Magnesium stearate, which can be derived from animals, was sourced from vegetable oil. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product containing ibuprofen lysine that could be considered a generic medicinal product of the reference product Nurofen Migraine Pain.

Comparative physico-chemical data, including *in vitro* dissolution and impurity profiles have been provided for the proposed product versus the reference product, and pharmaceutical equivalence has been shown.

A satisfactory account of the pharmaceutical development has been provided.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, 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 finished product. The results are satisfactory.

**Finished Product Specification**
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**  
The finished product is packaged in hard transparent polyvinylchloride/aluminium blister packs or in child resistant white opaque polyvinylchloride/aluminium blisters with a polyester layer. This product is available in pack sizes of 10 or 20 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

The Marketing Authorisation Holder has stated that not all pack sizes are intended for marketing. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.

**Stability of the product**  
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 3 years for both presentation types and the storage condition of “Store below 25°C”.

**Bioequivalence/bioavailability**  
A bioequivalence study was performed comparing the pharmacokinetic profiles of the test product Ibuprofen Lysine 342 mg Film-coated Tablets (INN-FARM d.o.o) versus the reference product Nurofen Migraine Pain. Suitable Certificates of Analysis have been provided for the test and reference products used in this study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**  
The SmPC, PIL and labels are acceptable from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. 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.

**Marketing Authorisation Application (MAA) form**  
The MAA form is satisfactory from a pharmaceutical perspective.

**Quality Overall Summary (Expert report)**  
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**  
The grant of a Marketing Authorisation is recommended.
III.2  NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of Ibuprofen Lysine 342 mg Film-coated Tablets 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.

Since Ibuprofen Lysine 342 mg Film-coated Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment, however an Environmental Risk Assessment was provided which was based upon published literature.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3  CLINICAL ASPECTS
Pharmacokinetics and Pharmacodynamics

With the exception of the following study, no new pharmacodynamic or pharmacokinetic data have been submitted with this application and none are required.

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

**An open-label, single centre, randomised, single-dose, two-way crossover bioequivalence study to compare and evaluate the pharmacokinetic profiles of the test product Ibuprofen Lysine 342 mg Film-coated Tablets (INN-FARM d.o.o) versus the reference product Nurofen Migraine Pain (342 mg ibuprofen lysine) in healthy, adult, male, human subjects under fasting conditions.**

Following an overnight fast subjects were dosed orally with either the test or reference product. Blood samples were taken pre-dose and up to 14 hours post dose. There was a washout period of 7 days between each dosing period.

A summary of the analysis of R-(-)-ibuprofen and S-(+)-ibuprofen results are presented in the tables below:
Table I: Summary of Pharmacokinetic Results for Each Treatment for S-(+) Ibuprofen

<table>
<thead>
<tr>
<th>Mean ± SD (CV%)</th>
<th>Plasma S-(+) Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ibuprofen Lysine</td>
</tr>
<tr>
<td>N</td>
<td>23</td>
</tr>
<tr>
<td>AUC_{0-1} (ng*hr/mL)</td>
<td>33732.56 ± 8248.07</td>
</tr>
<tr>
<td>(24.45)</td>
<td>(23.43)</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng*hr/mL)</td>
<td>34564.88 ± 8602.85</td>
</tr>
<tr>
<td>(24.89)</td>
<td>(23.80)</td>
</tr>
<tr>
<td>Residual Area (%)</td>
<td>2.32 ± 0.86</td>
</tr>
<tr>
<td>(%36.83)</td>
<td>(35.05)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>10295.55 ± 2030.50</td>
</tr>
<tr>
<td>(19.72)</td>
<td>(25.53)</td>
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<tr>
<td>T_{max} (hr)</td>
<td>0.500</td>
</tr>
<tr>
<td>(0.333 - 1.67)</td>
<td>(0.333 - 1.33)</td>
</tr>
<tr>
<td>K_{d} (1/hr)</td>
<td>0.2853 ± 0.0372</td>
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<tr>
<td>(13.04)</td>
<td>(10.81)</td>
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<tr>
<td>T_{1/2} (hr)</td>
<td>2.47 ± 0.32</td>
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<tr>
<td>(12.83)</td>
<td>(11.32)</td>
</tr>
</tbody>
</table>

*Median (Min - Max)
Profile of Subject 6 was excluded

Table II: Ratios and Confidence Intervals for S-(+) Ibuprofen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Comparisons</th>
<th>Ratio¹</th>
<th>Lower</th>
<th>Upper</th>
<th>Intra-Subject CV</th>
<th>Inter-Subject CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-1}</td>
<td>Test (A) - Reference (B)</td>
<td>99.06%</td>
<td>96.16%</td>
<td>102.06%</td>
<td>6.86%</td>
<td>25.12%</td>
</tr>
<tr>
<td>AUC_{0-inf}</td>
<td>Test (A) - Reference (B)</td>
<td>99.16%</td>
<td>96.27%</td>
<td>102.14%</td>
<td>6.80%</td>
<td>25.79%</td>
</tr>
<tr>
<td>C_{max}</td>
<td>Test (A) - Reference (B)</td>
<td>99.36%</td>
<td>91.57%</td>
<td>97.50%</td>
<td>16.13%</td>
<td>14.04%</td>
</tr>
</tbody>
</table>

¹Calculated using least-squares means according to the formula: \(\frac{e^{\text{Test} - \text{Reference}}} \times 100\).
²90% Geometric Confidence Interval using In-transformed data.
Table III: Summary of Pharmacokinetic Results for Each Treatment for R-(-) Ibuprofen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ibuprofen Lysine</th>
<th>Nurofen Migraine Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>( \text{AUC}_{0-t} ) (ng·hr/mL)</td>
<td>28856.75 ± 4483.10</td>
<td>28970.56 ± 4784.31</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ) (ng·hr/mL)</td>
<td>29256.59 ± 4554.60</td>
<td>29320.26 ± 4793.66</td>
</tr>
<tr>
<td>Residual Area (%)</td>
<td>1.36 ± 0.55</td>
<td>1.22 ± 0.54</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>11119.20 ± 2271.38</td>
<td>12162.61 ± 2270.94</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (hr)</td>
<td>0.500</td>
<td>0.500</td>
</tr>
<tr>
<td>( K_{\text{el}} ) (1/hr)</td>
<td>0.4025 ± 0.1195</td>
<td>0.4168 ± 0.1093</td>
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<tr>
<td>( T_{\frac{1}{2}, \text{el}} ) (hr)</td>
<td>1.90 ± 0.70</td>
<td>1.80 ± 0.60</td>
</tr>
</tbody>
</table>

*Median
(Min - Max)
Profile of Subject 6 was excluded

Table IV: Ratios and Confidence Intervals for R-(-) Ibuprofen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Comparisons</th>
<th>Ratio1</th>
<th>Lower</th>
<th>Upper</th>
<th>Intra-Subject CV</th>
<th>Inter-Subject CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{AUC}_{0-t} )</td>
<td>Test(A) - Reference(B)</td>
<td>98.80%</td>
<td>95.86%</td>
<td>103.90%</td>
<td>7.94%</td>
<td>14.18%</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} )</td>
<td>Test(A) - Reference(B)</td>
<td>99.94%</td>
<td>96.02%</td>
<td>104.02%</td>
<td>7.94%</td>
<td>14.17%</td>
</tr>
<tr>
<td>( C_{\text{max}} )</td>
<td>Test(A) - Reference(B)</td>
<td>90.93%</td>
<td>84.24%</td>
<td>98.14%</td>
<td>15.12%</td>
<td>14.12%</td>
</tr>
</tbody>
</table>

*1 Calculated using least-squares means according to the formula: \( \exp(\text{Test} - \text{Reference}) \times 100 \).

*2 90% Geometric Confidence Interval using ln-transformed
The 90% confidence interval of the test/reference ratio for log-transformed pharmacokinetic variables $C_{\text{max}}$, $\text{AUC}_{0-\infty}$, and $\text{AUC}_{0-72}$ were within the pre-defined limits of 80.00-125.00%, as specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). Therefore in conclusion, the applicant’s test product Ibuprofen Lysine 342 mg Film-coated Tablets is considered to be bioequivalent to the reference product Nurofen Migraine Pain.

**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 generated during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues arose from these studies.

**SmPC, PIL and Labels**

The SmPC, PIL and 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.

A Risk Management Plan has been developed to ensure that Ibuprofen Lysine 342 mg Film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for Ibuprofen Lysine 342 mg Film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.
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 a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of ibuprofen lysine 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 Ibuprofen Lysine 342 mg Film-coated Tablets and the relevant reference product.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labels are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and the reference product. Extensive clinical experience with ibuprofen lysine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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