Public Assessment Report

Decentralised Procedure

Ibuprofen Lysine 684 mg film-coated tablets

(ibuprofen lysine)

Procedure No: UK/H/6584/001/DC

UK Licence No: PL 34088/0048

ALKALOID-INT d.o.o.
Lay Summary
Ibuprofen Lysine 684 mg film-coated tablets
(Ibuprofen lysine)

This is a summary of the public assessment report (PAR) for Ibuprofen Lysine 684 mg film-coated tablets (UK/H/6584/001/DC; PL 34088/0048). It explains how Ibuprofen Lysine 684 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 684 mg film-coated tablets.

For ease of reading, this product will be referred to as Ibuprofen Lysine Tablets in this Lay Summary.

For practical information about using Ibuprofen Lysine Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Ibuprofen Lysine Tablets and what are they used for?
Ibuprofen Lysine tablets is a generic medicine. This means that Ibuprofen Lysine 684 mg film-coated tablets are similar to a ‘reference medicine’ already authorised in the UK called Nurofen Express 684 mg Caplets (Reckitt Benckiser Healthcare (UK) Ltd; PL 00063/0384).

Ibuprofen Lysine tablets are used for short-term symptomatic treatment of:
- mild to moderate pain such as headache, migraine, dental pain, dysmenorrhea, muscular pain, back pain and rheumatic pain
- fever
- feverishness and symptoms of cold and flu
Ibuprofen Lysine tablets are indicated for use in adults, and in adolescents above 12 years of age and weighing at least 40 kg.

How are Ibuprofen Lysine Tablets used?
Ibuprofen Lysine Tablets are taken by mouth. The whole tablet must be swallowed with water. Ibuprofen Lysine tablets have a break mark on one side. The score line is only there to help patients break the tablet if they have difficulty swallowing it whole.

Ibuprofen Lysine Tablets are for short term use only. Patients should take the lowest dose for the shortest time necessary to relieve the symptoms.

The recommended dose in adults and adolescents weighing from 40 kg (12 years and above) is 1 tablet, up to three times a day as required.

The recommended dose for adults and adolescents over 40 kg in weight (12 years and above) is one tablet (400 mg ibuprofen) up to 3 times a day, as required. There should be at least 6 hours between each dose. No more than 3 tablets (1200 mg ibuprofen) should be taken in any 24 hour period.

Ibuprofen Lysine Tablets should not be given to adolescents under 40 kg body weight or children under 12 years.

This medicine is supplied through a pharmacy.

For further information on how Ibuprofen Lysine Tablets are used, refer to the Summaries of Product Characteristics or package leaflet available on the MHRA website.

How do Ibuprofen Lysine Tablets work?
Ibuprofen Lysine Tablets contain the active substance, ibuprofen lysine, which belongs to a group of
medicines called non-steroidal anti-inflammatory drugs (NSAIDs). This product provides relief by changing the body’s response to headaches and migraine pain.

**How have Ibuprofen Lysine Tablets been studied?**
Because Ibuprofen Lysine Tablets is a generic medicine, studies in patients have been limited to tests to determine that the tablets are bioequivalent to the reference medicine, Nurofen Express 684 mg Caplets (Reckitt Benckiser Healthcare (UK) Ltd). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the benefits and risks of Ibuprofen Lysine Tablets?**
As Ibuprofen Lysine Tablets is a generic medicine that is bioequivalent to Nurofen Express 684 mg Caplets (Reckitt Benckiser Healthcare (UK) Ltd), the benefits and risks are taken as being the same as those for Nurofen Express 684 mg Caplets (Reckitt Benckiser Healthcare (UK) Ltd).

**Why are Ibuprofen Lysine Tablets approved?**
It was concluded that, in accordance with EU requirements, Ibuprofen Lysine Tablets have been shown to have comparable quality and to be bioequivalent to Nurofen Express 684 mg Caplets (Reckitt Benckiser Healthcare (UK) Ltd). Therefore, the view was that, as for Nurofen Express 684 mg Caplets (Reckitt Benckiser Healthcare (UK) Ltd) the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Ibuprofen Lysine Tablets?**
A risk management plan has been developed to ensure that Ibuprofen Lysine Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Ibuprofen Lysine Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Ibuprofen Lysine Tablets**
Bulgaria, Croatia, the Czech Republic, Hungary, Italy, Poland, Romania, the Slovak Republic, Slovenia and the UK agreed to grant a Marketing Authorisation for Ibuprofen Lysine Tablets on 04 January 2018. A Marketing Authorisation was granted in the UK on 19 January 2018.

The full PAR for Ibuprofen Lysine Tablets follows this summary.

This summary was last updated in November 2018.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMS) considered that the application for Ibuprofen Lysine 684 mg film-coated tablets (UK/H/6584/001/DC; PL 34088/0048), is approvable.

The product is supplied through a pharmacy (as a P medicine) and is indicated for short-term symptomatic treatment of mild to moderate pain such as headache, migraine, dental pain, dysmenorrhea, muscular pain, back pain, rheumatic pain, fever and symptoms associated with the common cold and influenza.

Ibuprofen Lysine tablets are indicated for use in adults, and in adolescents above 12 years of age and weighing at least 40 kg.

This application was submitted using the Decentralised Procedures (DCP) with the UK as the RMS and Bulgaria, Croatia, the Czech Republic, Hungary, Italy, Poland, Romania, the Slovak Republic and Slovenia as CMSs. The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross referred to Nurofen Express 684 mg Caplets, originally authorised to Crookes Healthcare Limited (PL 00327/0143) on 17 January 2006. This licence underwent a change of ownership procedure to the current Marketing Authorisation holder, Reckitt Benckiser Healthcare (UK) Ltd (PL 00063/0384), on 19 April 2011.

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swelling and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation. Following oral administration, ibuprofen lysine dissociates into 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.

Clinical evidence demonstrates that when 1-tablet dose of 684 mg ibuprofen lysine (equivalent to 400 mg ibuprofen) is taken the pain-relieving effects can last for up to 8 hours.

No new non-clinical studies were conducted, which is acceptable given that this is a generic application of an originator product that has been in clinical use for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

A bioequivalence study was submitted to support this application comparing the test product, Ibuprofen Lysine 684 mg film-coated tablets versus the reference product, Nurofen Express 684 mg Caplets (Reckitt Benckiser Healthcare (UK) Ltd), in healthy adult male subjects under fasting conditions. The applicant has stated that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP), including International Conference on Harmonisation (ICH) guidelines, Directive 2001/20/EC of the European Parliament and the most recent version of the declaration of Helsinki.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.
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.

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.

For manufacturing sites outside the Community, the RMS 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.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 04 January 2018). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 34088/0048) for this product on 19 January 2018.
II QUALITY ASPECTS

II.1 Introduction
The product is presented as a film-coated tablet. Each tablet contains 684 mg ibuprofen lysine (equivalent to 400 mg ibuprofen), as active ingredient. The excipients present are silicified microcrystalline cellulose, copovidone, sodium starch glycolate (type A) and magnesium stearate making up the tablet core. The film-coat is composed of Opadry II White (hypromellose, titanium dioxide (E171), polydextrose, talc, maltodextrin and triglycerides, medium-chain).

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of Opadry II White which complies with an in-house specification.

None of the excipients used contain material of animal or human origin. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

The finished product is packed in blisters formed from white polyvinylchloride (PVC)/polyvinylidenechloride (PVdC)/aluminium (Al) foil or in alternative child-resistant white PVC/PVdC/Al foil fortified with polyethylene terephthalate (PET) layer.

Ibuprofen Lysine 684 mg film-coated tablets are available in blister packs containing 10, 12, 20 and 24 tablets.

Not all pack sizes may be marketed.

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 food.

II.2 Drug Substance
INN: ibuprofen lysine
Chemical name: Lysine salt of 2(4-isobutylphenyl) propionic acid
Structure:

![Chemical Structure of Ibuprofen Lysine]

Molecular formula: \( \text{C}_{19}\text{H}_{32}\text{N}_2\text{O}_4 \)
Molecular mass: 352.4 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.

Ibuprofen lysine is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials 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 have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 **Medicinal Product**
**Pharmaceutical Development**
The objective of the development programme was to develop a generic equivalent of Nurofen Express 684 mg Caplets (Reckitt Benckiser Healthcare (UK) Ltd).

Comparative dissolution profiles have been presented for the proposed and reference products.

**Manufacture of the products**
A satisfactory batch formula has been provided for the manufacture of the product along with an appropriate description of the manufacturing process. The manufacturing process has been validated at production scale and has shown satisfactory results.

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

**Stability of the product**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results a shelf life of 2 years with a storage condition ‘Store below 30°C’ are set. These are satisfactory.

**Bioequivalence/bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

II.4 **Discussion on chemical, pharmaceutical and biological aspects**
The grant of a Marketing Authorisation is recommended.
III    NON-CLINICAL ASPECTS

III.1  Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen lysine are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2  Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3  Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4  Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5  Environmental Risk Assessment (ERA)
The applicant has provided a Phase II Tier B assessment for Ibuprofen Lysine 684 mg film-coated tablets. This is acceptable.

III.6  Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical point of view.

IV    CLINICAL ASPECTS

IV.1  Introduction
The clinical pharmacology of ibuprofen lysine is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of ibuprofen lysine.

Based on the data provided, Ibuprofen Lysine 684 mg film-coated tablets can be considered bioequivalent to Nurofen Express 684 mg Caplets (Reckitt Benckiser Healthcare (UK) Ltd).

IV.2  Pharmacokinetics
In support of this application, the Marketing Authorisation Holder has submitted results from the following bioequivalence study conducted under fasting conditions.

Study
This was a randomised, open label, two-way crossover bioequivalence study comparing the test product Ibuprofen Lysine 684 mg film-coated tablets with the reference product Nurofen...
Express 684 mg Caplet (Reckitt Benkiser Healthcare (UK) Ltd) in healthy, adult, male, human subjects under fasting conditions.

A single dose of 684 mg of test and reference formulation was administered in each period. Blood samples were collected pre-dose and, up to and including 14.00 hours post-dose. The washout period was 7 days.

**Results**

**Geometric Least Square Mean, Ratios and 90% Confidence Interval for ibuprofen lysine (S-ibuprofen)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric Mean Ratio Test/Ref</th>
<th>Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-t}</td>
<td>99.21%</td>
<td>96.15%-102.36%</td>
</tr>
<tr>
<td>AUC_{0-inf}</td>
<td>99.95%</td>
<td>96.73%-103.28%</td>
</tr>
<tr>
<td>C_{max}</td>
<td>103.00%</td>
<td>96.78%-109.63%</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for C_{max} and AUC for ibuprofen lysine (S-ibuprofen) were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Ibuprofen Lysine 684 mg film-coated tablets) and the reference formulation, Nurofen Express 684 mg Caplets (Reckitt Benckiser Healthcare (UK) Ltd) in healthy adult subjects, under fasting conditions.

**IV.3 Pharmacodynamics**

No new data have been submitted and none are required for applications of this type.

**IV.4 Clinical efficacy**

No new efficacy data have been submitted and none are required for applications of this type.

**IV.5 Clinical safety**

The safety of ibuprofen lysine is well known. No new safety data were submitted and none are required.

**IV.6 Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Atenolol tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the current RMP, are listed below:
Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended.

V User consultation
The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet (PIL) was English.

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.

IV OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and the reference product. The benefit-risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The current approved labelling for Ibuprofen Lysine 684 mg film-coated tablets (PL 34088/0048) is presented below:
PAR Ibuprofen Lysine 684 mg film-coated tablets

Ibuprofen lysine is used to treat short-term symptoms of inflammation, such as headache, muscle pain, dental pain, dysmenorrhea, premenstrual pain, back pain, breast pain,テンバールパーカ, fever, and muscle and joint pain.

Dosage: Irritable bowel syndrome and short-term use only. Take the lowest dose for the shortest time necessary to relieve your symptoms. For adults and adolescents weighing from 40 kg: Take 1 tablet with water, up to three times a day as needed. For at least 3 days before symptoms.

Do not take more than 3 tablets (2100 mg Ibuprofen) in 24 hours.

Do not give to children weighing under 40 kg and children under 12 years of age.

In children and adolescents between 12 and 16 years the medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

In adults, you should consult a doctor if symptoms persist or are severe, or if the product is required for more than 1 day when treating pain and 3 days when treating inflammation or fever. Warning: Do not take more medicine than the label tells you to.

Do not take if:
- you are allergic to Ibuprofen or any other ingredient of the product,
- you have had a stomach ulcer or peptic ulcer disease
- you have had a blood disorder such as leukemia, aplastic anemia, or other related blood disorders
- you have taken other NSAIDs or are taking aspirin or disodium glycocholic acid with a daily dose above 30 mg
- you have stomach pain or heartburn even if it is mild or occasional
- you are pregnant
- you are breastfeeding
- you have an ulcer or peptic ulcer disease
- you have a history of peptic ulcer disease
- you are taking other medications that may increase the risk of bleeding
- you have had a recent large surgical procedure or are taking aspirin
- you have a history of stomach bleeding
- you have a history of kidney disease
- you have a history of liver disease
- you have a history of high blood pressure

Keep out of the sight and reach of children.

Each tablet contains 684 mg of Ibuprofen lysine (equivalent to 400 mg ibuprofen).

See label for further information.

For oral use. Store below 30°C.

MA Holder: Alkaloid d.o.o., Šendirjeva ulica 4, 1211 Ljubljana - Coma, Slovenia

PL 34889/1048

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# Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval / non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To widen the current approved indications of the medicinal product Ibuprofen lysine 684 mg film-coated tablets in line with the currently approved ibuprofen medicinal products indications in the European Community. Consequently, sections 4.1 and 4.2 of the SmPC, sections 1 and 3 of the PL, and point 15 of the Labelling have been updated. An updated RMP version has also been submitted.</td>
<td>UK/H/6584/001/II/002</td>
<td>SmPC, PIL and labelling</td>
<td>27/03/2018</td>
<td>04/10/2018</td>
<td>Approved</td>
<td>Yes-see Annex 1</td>
</tr>
</tbody>
</table>
I. Recommendation

Based on the review of the data, and assessment of responses to the request for supplementary information, the RMS considers that the variation for IBUPROFEN LYSINE 684 mg film-coated tablets (ibuprofen lysine), in the treatment of “short-term symptomatic relief of headache and migraine”, is approvable.

II. Executive Summary

II.1 Scope of the variation

This Mutual Recognition Type II variation concerns Ibuprofen Lysine 684 mg film-coated tablets.

This product was authorised under Article 10(1) via DCP (Day 210 4 January 2018; granted 19 January 2018) with UK as RMS, and BG, HR, CZ, HU, IT, PL, RO, SK and SI as CMSs. The present variation is submitted with UK as RMS and all CMSs mentioned above.

This Type II variation application is submitted in the following category:

C.I.6 Change(s) to therapeutic indication(s)
   (a)  Addition of a new therapeutic indication or modification of an approved one.

The reference product for this product is Nurofen Express 684 mg (PL 00063/0384) by Reckitt Benckiser Healthcare (UK) Ltd.

The following changes to sections 4.1 and 4.2 of the SmPC are proposed:
<table>
<thead>
<tr>
<th>Section 4.1</th>
<th>Short-term symptomatic relief of headache and migraine.</th>
<th>Section 4.1</th>
<th>Short-term symptomatic treatment of mild to moderate pain such as headache, migraine, dental pain, dysmenorrhea, muscular pain, back pain, rheumatic pain, fever and symptoms associated with the common cold and influenza.</th>
<th>Section 4.1</th>
<th>For the relief of headache and migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen Lysine is indicated for use in adults, adolescents above 12 years of age and weighing at least 40 kg.</td>
<td>&lt;Product name&gt; is indicated for use in adults, adolescents above 12 years of age and weighing at least 40 kg.</td>
<td>Ibuprofen Lysine is indicated for use in adults, adolescents above 12 years of age and weighing at least 40 kg.</td>
<td>&lt;Product name&gt; is indicated for use in adults, adolescents above 12 years of age and weighing at least 40 kg.</td>
<td>Ibuprofen Lysine is indicated for use in adults, adolescents above 12 years of age and weighing at least 40 kg.</td>
<td>&lt;Product name&gt; is indicated for use in adults, adolescents above 12 years of age and weighing at least 40 kg.</td>
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<tr>
<td>Section 4.2</td>
<td>Posology</td>
<td>Section 4.2</td>
<td>Posology</td>
<td>Section 4.2</td>
<td>For oral administration and short-term use only.</td>
</tr>
<tr>
<td>Adults and adolescents ≥40 kg (12 years of age and above):</td>
<td>Adults and adolescents ≥40 kg (12 years of age and above):</td>
<td>Adults and adolescents ≥40 kg (12 years of age and above):</td>
<td>Adults and adolescents ≥40 kg (12 years of age and above):</td>
<td>Adults and adolescents ≥40 kg (12 years of age and above):</td>
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<tr>
<td>Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).</td>
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<tr>
<td>The patient should consult a doctor if symptoms worsen, or if the product is required for more than 3 days.</td>
<td>If in children and adolescents between 12 and 18 years this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.</td>
<td>The patient should consult a doctor if symptoms persist or worsen, or if the product is required in adults for more than 10 days.</td>
<td>If in children and adolescents this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.</td>
<td>The patient should consult a doctor if symptoms persist or worsen, or if the product is required in adults for more than 10 days.</td>
<td>If in children and adolescents this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.</td>
</tr>
<tr>
<td>The recommended dose is 1 tablet, taken with water, up to three times a day as required.</td>
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<td>Leave at least 6 hours between doses.</td>
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<td>Leave at least 6 hours between doses.</td>
<td>Leave at least 4 hours between doses.</td>
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<td>Do not take more than 3 tablets (1200 mg ibuprofen) in any 24 hour period.</td>
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<td>Do not take more than 3 tablets (1200 mg ibuprofen) in any 24 hour period.</td>
<td>Do not take more than 3 caplets in any 24 hour period.</td>
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<td>Special patient groups</td>
<td>Special patient groups</td>
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<tr>
<td><strong>Paediatric population:</strong>&lt;br&gt;Ibuprofen Lysine is contraindicated in adolescents weighing under 40 kg or children under 12 years of age (see section 4.3).</td>
<td><strong>Paediatric population:</strong>&lt;br&gt;&lt;Product name&gt; is contraindicated in adolescents weighing under 40 kg or children under 12 years of age (see section 4.3).</td>
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<tr>
<td><strong>Elderly:</strong>&lt;br&gt;No special dose adjustment is required. Because of the possible undesirable-effect profile (see section 4.4), it is recommended to monitor the elderly particularly carefully.</td>
<td><strong>Elderly:</strong>&lt;br&gt;No special dose adjustment is required. Because of the possible undesirable-effect profile (see section 4.4), it is recommended to monitor the elderly particularly carefully.</td>
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<tr>
<td><strong>Renal impairment:</strong>&lt;br&gt;No dose reduction is required in patients with mild to moderate impairment to renal function (patients with severe renal insufficiency, see section 4.3).</td>
<td><strong>Renal impairment:</strong>&lt;br&gt;No dose reduction is required in patients with mild to moderate impairment to renal function (patients with severe renal insufficiency, see section 4.3).</td>
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<tr>
<td><strong>Hepatic impairment (see section 5.2):</strong>&lt;br&gt;No dose reduction is required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction, see section 4.3).</td>
<td><strong>Hepatic impairment (see section 5.2):</strong>&lt;br&gt;No dose reduction is required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction, see section 4.3).</td>
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</tr>
<tr>
<td><strong>Method of administration</strong>&lt;br&gt;For oral administration and short-term use only.&lt;br&gt;The film-coated tablet should be taken with water.&lt;br&gt;It is recommended that patients with sensitive stomachs take Ibuprofen Lysine with food.</td>
<td><strong>Method of administration</strong>&lt;br&gt;For oral administration and short-term use only.&lt;br&gt;The film-coated tablet should be taken with water.&lt;br&gt;It is recommended that patients with sensitive stomachs take &lt;Product name&gt; with food.</td>
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</table>
III. Scientific discussion

III.1 Clinical aspects

The indications/therapeutic uses proposed for Ibuprofen lysine 684 mg film-coated tablets have already been approved for ibuprofen medicinal products in the European Community. Consequent to the proposed widening of the indication for various types of mild to moderate pain, a recommendation on the duration of treatment for these conditions is added in 4.2 Posology and method of administration in the SmPC and consequently in the Patient Leaflet and Labelling.

The MAH states that the reference medicinal product indications are not harmonised between EU Member States, and among the RMS and CMSs. Additionally, the active substance ibuprofen has an established clinical use on the EU market, which is further supported by published clinical data for a wider scope of therapeutic use than the one approved for Alkaloid’s generic product. The MAH thus considers that the request for expansion of the indications justified, and of public health interest.

No new clinical studies are submitted.

The Applicant has provided two separate justifications in support of the proposed variation: (i) a regulatory justification on the grounds of established indications for other ibuprofen products in the EU; and (ii) a scientific justification via the submission of an ‘Addendum to the Clinical Overview’, dated February 2018, providing evidence for the use of ibuprofen in the proposed wider indications.

Key aspects of this supporting evidence are summarised in this variation assessment report.

Regulatory justification

The rationale of the proposed change in the approved therapeutic indication is that the proposed use of Alkaloid’s ibuprofen lysine product is already widely recognised and approved in EU. The MAH states that the proposed indications are well supported with published clinical literature data and approved in similar products (active substance: ibuprofen), originator and generic in EU. The MAH further states that change is in-line with the approved legal status (i.e. product not subject to medical prescription) for this product and is in accordance with the MHRA Guideline for ibuprofen products. A patient safety justification is included, stating that by extension of the indications to match the established uses of ibuprofen products elsewhere, they would avoid potential confusion in patients caused by the limited indication currently approved in the Ibuprofen lysine 684 mg film-coated tablets by Alkaloid.

Furthermore, the reference product Nurofen 684 mg tablets, to which the initial generic application for Ibuprofen lysine 684 mg film-coated tablets refers, is authorised in January 2006 via national procedures in many Member States across EU. The MAH has provided a table to demonstrate that whilst the composition of the products is identical among the MS; the approved indications are not harmonised, and all are wider than those approved in UK reference medicinal product, and those approved in Alkaloid’s current product.

As all the national Marketing Authorisations of the reference products fall under the scope of the same Global Marketing Authorisation to which the current product refers, all the product information of the authorised Nurofen (ibuprofen lysine) 400 mg film coated tablets authorised across MS are in support of the change of the indication. The wider set of indications as proposed in this variation has already been approved in Nurofen brand ibuprofen lysine products in other European MS.
Assessor comments
The initial approval of this product was through the DCP UK/H/6584/001/DC, granted in January 2018. The chosen reference product for this Article 10(1) procedure, and also the product against which bioequivalence was demonstrated in the submitted study is Nurofen Express 684 mg Caplets (Reckitt Benckiser Healthcare (UK) Ltd), with the indications of headache and migraine only.

As discussed during the original DCP, RMS UK acknowledged the lack of harmonisation of indications for the equivalent (nationally authorised) reference products across CMSs. However, in line with the 10(1) legal basis of the DCP, the product information was to be aligned with the chosen regulatory reference product in the RMS (UK). This was agreed.

The applicant could have chosen a European Reference Product for the original DCP, and consequently gained approval for a broader indication from the outset. However, the MAH chose the UK product, and stated their intention to submit a clinical variation after the DCP in order to widen the scope of the indications, and that is what is proposed with the current variation. As per the Day 180 Clinical

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**Table: Paracetamol Lysine 684 mg film-coated tablets UK/H/6584/001/DC**

<table>
<thead>
<tr>
<th>Country</th>
<th>Product name, MAH, date of first authorisation</th>
<th>Active substance</th>
<th>Ph. Form</th>
<th>Strength</th>
<th>Indication</th>
</tr>
</thead>
</table>
| BE      | NUROFEN 400
FASTTABS 400 mg, compacts pelliculés.
Reckitt Benckiser
Healthcare (Belgium)
12/07/2002
MA No: BE235551 | ibuprofen lysine | film-coated tablets | 400 mg | Symptomatic treatment of mild to moderate pain, such as headache, menstrual pain, muscle pain and dental pain. Symptomatic treatment of fever (SmPC NUROFEN 400 FASTTABS, 2015) |
| AT      | Nurofen rapid 400 mg - Filatublettene, Reckitt
Benckiser Deutschland GmbH, 15.09.2000
MA No: Z. Nr.: 1-23773 | ibuprofen lysine | film-coated tablets | 400 mg | Painful conditions (e.g., back pain, toothache, muscle pain, joint pain, menstrual pain, nerve pain)
For the treatment of the acute headache phase in migraine with and without aura and the treatment of tension headaches
- Pain in colds and flu. (SmPC Nurofen rapid, 2010) |
| FR      | NUROFENFLASH 400 mg, comprimé pelliculé
MAH: RECKITT BENCKISER
HEALTHCARE FRANCE, 12/01/2005 | ibuprofen lysine | film-coated tablets | 400 mg | This medication contains a non-steroidal anti-inflammatory drug: ibuprofen. In adults and children over 30 kg (approximately 11-12 years of age), in the short-term treatment of fever and/or pain, such as:
- headache.
- influenza.
- dental pain.
- aches.
- painful periods.
It is indicated in adults in the treatment of mild to moderate migraine attack with or without aura after a medical opinion. (SmPC RUROFENFLASH, 2017) |
| PL      | Nurofen Express TAB 400 mg, 400 mg, tablette
powlekane, MAH: Reckitt Benckiser (Poland) S.A.
11/12/2008, MA No: 12553 | ibuprofen lysine | film-coated tablets | 400 mg | Severe headache in the course of migraine with or without aura. Tension headache. Painful conditions (e.g., back pain, dental pain, muscle pain, joint pain, dysmenorrhea, neuralgia).
Pain in the course of colds and flu. (SmPC Nurofen Express TAB, nd.) |
| DE      | Nurofen Immedia 400 mg
Filtablatten MAH: Reckitt Benckiser Deutschland GmbH, 18.09.2003
43917 01 00 | ibuprofen lysine | film-coated tablets | 684 mg | Symptomatic treatment of:
- Mild to moderate pain, such as headaches, toothaches and menstrual pain
- fever (SmPC Nurofen Immedia, 2015) |
| PT      | Nurofen Migexpress MAH:
Reckitt Benckiser Healthcare, Lda
06/11/2017, MA No:
5731773, 5731807 | ibuprofen lysine | film-coated tablets | 400 mg | Nurofen Migexpress is indicated for adults:
In mild to moderate pain, headache, migraines, dental pain, menstrual pain, muscle pain, rheumatic pain, back pain, neuralgia and symptoms of constipation and the flu.
And in the symptomatic treatment of fever lasting less than 3 days. (SmPC Nurofen Migexpress, 2017) |
Assessment Report for UK/H/6584/001/DC, a subsequent variation application to widen the scope of indications should be supported by appropriate data and will be subject to assessment.

A regulatory justification based upon a broader range of indications in CMSs than the RMS is therefore unacceptable, as the legal basis of the application under 10(1) requires alignment with the Reference product, which in this case is the UK version of Nurofen Express PL 00063/0384.

It is, however, acknowledged that the national Marketing Authorisations of the reference products fall under the scope of the same Global Marketing Authorisation (MAH-Reckitt Benckiser). A list of MSs has been provided for whom the nationally authorised version of the reference product includes a broader range of indications than the RMS UK version. It is noted that of this list, only Poland is a CMS in the current procedure, and the indications in Poland are in line with the proposed widened indication in RMS UK.

Nonetheless, the assessment of the current variation is based primarily on upon the scientific justification provided by the applicant, with the supplied evidence for use of the product in the proposed indications presented as literature data in lieu of new clinical studies.

The MAH has also provided a list of ibuprofen products registered to Reckitt Benckiser Healthcare under the Nurofen brand with a broad range of indications, including:

- Nurofen 400 mg Capsule Soft (PL 00063/0615)
- Nurofen 400 mg Tablets (PL 00063/0722)
- Nurofen Express 400 mg Liquid Capsules (PL 00063/0653)
- Nurofen Express 400 mg Oral Powder (PL 00063/0616)
- Nurofen Maximum Strength Migraine Pain 684 mg Caplets and Nurofen Express 684 mg Caplets (PL 00063/0384)
- Nurofen Express Soluble 400 mg Oral Powder (PL 00063/0611)

**Assessor comments**

With the exception of the ibuprofen lysine PL 00063/0384, which is the reference product in the current procedure and is indicated solely for headache and migraine, the other Nurofen products listed are reported with a broader range of indications.

The ibuprofen lysine products on the list (PL 00063/0616 and PL 00063/0611) were previously approved in the UK, but cancelled by the MAH in November 2017.

The other products on this list (PL 00063/0615, PL 00063/0722 and PL 00063/0653) are ‘standard’ ibuprofen rather than ibuprofen lysine.

MAH states that generic ibuprofen lysine 400 mg product approved with indication similar to those proposed in this application is Ibusoft/Ibusan, authorised through procedures: UK/H/5306/001-002/DC & 5307/001-002/DC. Ibusoft 400mg capsules are indicated for symptomatic relief of headaches, migraine, dental pain, backache, dysmenorrhoea, muscular pain, neuralgia, non-serious arthritic conditions, rheumatic pain, feverishness, colds and influenza.

The proposed indications are reportedly in-line with the MHRA guideline for ibuprofen products.

The MAH argues that the well-established use of ibuprofen (regardless of salts/esters) by patients in EU Member states must also be taken into consideration, as well as the risk of confusion and off-label use due to established practises for self-medication.
Assessor comments
The products referred to by the MAH, namely Ibusoft/Ibusan, authorised through UK/H/5306/001-002/DC and UK/H/5307/001-002/DC are not ibuprofen lysine products. This is stated in the Public Assessment Reports for these products, and in the SmPC.

The current product is licensed in the UK with the legal status ‘P’, i.e. available from a pharmacy without requirement for a medical prescription. The proposed indication is “short term symptomatic treatment of mild to moderate pain such as headache, migraine, dental pain, dysmenorrhoea, muscular pain, back pain, rheumatic pain, fever, symptoms associated with the common cold and influenza”. These conditions are all in line with MHRA guidance on ibuprofen lysine with a ‘P’ OTC classification, and therefore if approved, would not affect the legal status of the product in UK.

III.3.1 Clinical pharmacology

No new clinical pharmacology data are provided.

Pharmacodynamics related to proposed indications

Ibuprofen lysine is the lysine salt of ibuprofen, a propionic acid derivative, having analgesic, anti-inflammatory and antipyretic activity. Following oral administration, ibuprofen lysine dissociates to ibuprofen acid and lysine. Lysine has no recognized pharmacological activity. The pharmacological properties of ibuprofen lysine, therefore, are the same as those of ibuprofen acid.

Ibuprofen inhibits both COX-1 and COX-2 isoenzymes. NSAIDs appear to exert anti-inflammatory, analgesic and antipyretic activity through inhibition of COX-2 isoenzyme. Analgesic activity of ibuprofen appears to be mediated principally through inhibition of the COX-2 isoenzyme with subsequent reduction in the synthesis of certain prostaglandins from their arachidonic acid precursors (AHFS, 2009).

Assessor comments
The pharmacodynamic aspects of ibuprofen lysine presented by the applicant are representative of text within section 5.1 of the approved SmPC, and the corresponding section 5.1 of the reference product SmPC. This is agreed.

Most pharmacokinetic data relating to ibuprofen acid also apply to ibuprofen lysine. However, there are well-known pharmacokinetic differences between ibuprofen and ibuprofen lysine, most notably in the absorption kinetics and $t_{\text{max}}$. A discussion on the pharmacokinetic properties of ibuprofen lysine relative to ibuprofen acid is provided in the original Clinical Overview.

III.3.2 Clinical efficacy

No new clinical efficacy data are provided.

The MAH states that according to available Best Practice Guidelines for treatment of pain in different conditions, ibuprofen is recommended as primary and secondary treatment option, due to a superior efficacy and lowest risk of adverse effects in comparison with other NSAIDs, as well as other analgesics.
Ibuprofen is used for an ever-increasing range of clinical conditions and because of its reliable analgesic activity and good safety it is approved in a number of countries for over-the-counter (OTC) self-medication of a variety of minor painful conditions, mainly headaches, migraine, muscular rheumatism, period pains, toothache and cold/flu symptoms.

Low-dose, OTC ibuprofen has been used for pain relief for over 30 years without any major health issues. An author’s review of ibuprofen in acute pain suggested that rapidly absorbed formulations of salts, or features to speed absorption, provided better analgesia than standard ibuprofen as the free acid. Fast-acting formulations of ibuprofen demonstrated more rapid absorption, faster initial pain reduction, good overall analgesia in more patients at the same dose, and probably longer-lasting analgesia, but with no higher rate of patients reporting adverse events. Formulation chemistry is of potential importance for analgesics.

A review of eighty-five studies that directly compared ibuprofen to acetaminophen revealed that, for the most part, ibuprofen was more efficacious than acetaminophen for the treatment of pain and fever in both paediatric and adult populations, and that these two drugs were equally safe.

One author summarised 18 double-blind clinical trials, comparing the efficacy of ibuprofen with other analgesics as aspirin, codeine and propoxyphene. Six of them provide strong evidence of analgesic activity in at least two pain models, especially for mild to moderate pain, in patients with dental pain due to tooth extractions, dysmenorrhea and episiotomy pain. Ibuprofen is as effective or more effective than aspirin, codeine or propoxyphene.

A blinded, multicentre study in general practice of up to 7 days of aspirin, paracetamol (both up to 3 g daily) or ibuprofen (up to 1.2 g daily), administered for common painful conditions, regarding the rate of significant adverse events found that ibuprofen was statistically equivalent to paracetamol and that both were significantly better tolerated than aspirin. The main indications were musculoskeletal or back pain (48%), sore throat, the common cold and flu (31%). Total gastrointestinal events (including dyspepsia) and abdominal pain were less frequent with ibuprofen (4 and 2.8%, respectively) than with paracetamol (5.3 and 3.9%) or aspirin (7.1 and 6.8%). Since overall tolerability of ibuprofen in this large-scale study was equivalent to that of paracetamol and better than that of aspirin, it was suggested that for the short-term management of painful conditions in general practice, ibuprofen could be recommended as a first-line analgesic, because of the poor tolerability of aspirin and the potential risks of paracetamol overdose.

Assessor comments
These literature references provide supportive data for the well-known analgesic effect of ibuprofen, which is not disputed.

Approval of new indication(s) requires specific data pertaining to those indications, provided either through clinical studies with the current product, or with reference to appropriate literature in lieu of new clinical studies. The MAH has provided a selective literature review in support of the role of ibuprofen for each of the proposed indications (see below for summary and assessment).

Dental pain
The MAH cites BMJ Best Practice guidance for dental abscess, referring to ibuprofen 400 mg every 4-6 hours (when required), up to a maximum of 2400 mg daily.

In addition, the following studies are cited in support of ibuprofen in dental pain:

A review of 72 randomised, double-blind, placebo-controlled trials of ibuprofen (any formulation) and placebo with moderate to severe post-operative pain, including 57 studies with dental pain following
extraction of one or more impacted third molars. In dental surgery, nine studies used lysine, arginine or other ‘soluble’ salts. The proportion of participants with at least 50% pain relief was 10% (41/409) for placebo and 66% (361/550) for ibuprofen 400 mg.

**Assessor comments**
The data from the submitted review supports ibuprofen, including soluble salts, as superior to placebo in the treatment of dental pain.

Another review included 2241 subjects in seven studies evaluating ibuprofen in post-operative dental pain.

**Assessor comments**
For the studies in the submitted, only one included ibuprofen lysine, which was superior to placebo in pain relief scores, and with faster/more effective analgesic effect than paracetamol.

In general, these data provide evidence that ibuprofen in the commonly prescribed dose 400 mg (equivalent to the current product), has analgesic effect superior to placebo and to 1000 mg paracetamol, and a faster onset of action compared to paracetamol.

One study group assessed the effects of pre-operative analgesics for pain relief in children and adolescents undergoing dental treatment, and included 4 studies.

One trial reported no statistical difference in postoperative pain experienced by the ibuprofen group and the control group for children undergoing dental treatment. Data from two trials, including patients who were having orthodontic separator replacement without a general anaesthetic, were pooled to determine the effect of preoperative ibuprofen on the severity of postoperative pain. There was a statistically significant benefit, with regard to severity of postoperative pain, for giving ibuprofen preoperatively with mean difference -19.12 (95% CI -29.36 to -8.87; P = 0.0003; moderate quality evidence) on a visual analogue scale (0 to 100) indicating a probable benefit for preoperative ibuprofen before this orthodontic procedure.

**Assessor comments**
One study used patients aged 6-12 years, using a paediatric preparation of 100 mg/5ml ibuprofen and so cannot be directly applied to the indicated population for the current ibuprofen lysine tablets.

Another study had a mean age of patients of 7 years, significantly younger than the indicated population for the current product.

The results of the studies by two authors are insufficiently described to provide support the current product for an indication of dental pain in the paediatric/adolescent population (>12 years).

A further 15 studies are presented in support of ibuprofen for the indication of dental pain.

**Assessor comments**
For studies comparing ibuprofen vs placebo in dental pain, none of the reported studies used ibuprofen lysine, and only studies by three authors used ibuprofen with comparable posology to the current product. Data from the additional studies may be considered supportive. Nonetheless, these studies provide some evidence that ibuprofen is more effective than placebo for providing analgesia in painful dental conditions in adults. No data is provided in these studies for children/adolescents.
For studies comparing ibuprofen to other drugs, none of the reported studies used ibuprofen lysine. These data do provide some supportive evidence for ibuprofen 400 mg, equivalent to the current product, as superior to diclofenac for analgesia effect, onset and duration in patients following removal of impacted mandibular third molars. In addition, the studies by two authors provide evidence of superiority of ibuprofen 400 mg over a combination ASA/codeine/caffeine product and placebo for analgesic effect in post-operative dental pain, and superior to celecoxib for analgesia following oral surgery.

**Conclusions on dental pain**

It is acknowledged that published clinical guidelines refer to the use of ibuprofen in dental pain, and other comparable products include this indication. The MAH has provided limited data specifically regarding ibuprofen lysine in dental pain. One review is stated to include data on soluble ibuprofen salts, and one study included ibuprofen lysine.

It is considered that sufficient evidence is provided to support the use of ibuprofen in the indication of dental pain.

**Dysmenorrhoea**

The MAH states that there is evidence-based support for the efficacy of COX-inhibitors, including ibuprofen, in primary dysmenorrhoea. BMJ Best Practice – painful periods (2017) recommends OTC NSAIDs including ibuprofen for analgesia in women with painful periods.

**Assessor comments**

UK NICE clinical knowledge summary recommends use of NSAIDs in dysmenorrhoea, based upon expert opinion from guidelines published by the Royal College of Obstetricians and Gynaecologists, the European Association of Urology, and Cochrane review, with insufficient evidence to indicate whether one NSAID is more effective than others.

A Cochrane review is presented to provide data for use of ibuprofen in dysmenorrhoea. The review included 6 trials comparing ibuprofen to placebo, 2 trials comparing ibuprofen to paracetamol, and 5 trials comparing ibuprofen to other NSAIDs.

**Assessor comments**

For studies comparing ibuprofen with placebo, none of the reported studies in the Cochrane review are stated as using ibuprofen lysine. Three of the 6 studies reported used ibuprofen 400 mg, equivalent to the current product, and demonstrated superiority over placebo. The additional studies are supportive. None of the studies included children or adolescents ≥12 and <15 years.

For ibuprofen compared to paracetamol, neither of the reported studies in the Cochrane review are stated as using ibuprofen lysine. One of the 2 studies reported used ibuprofen 400 mg, equivalent to the current product. The magnitude of the “favourable effect” over paracetamol is not stated. Neither of the studies included adolescents or children <18 years.

For ibuprofen compared to other NSAIDs, the formulation/posology of the ibuprofen in one study is not provided. Ibuprofen 400 mg was inferior to diclofenac 50 mg in terms of efficacy, but with a better safety profile and ibuprofen 1200 mg daily was superior to naproxen. The dosing of ibuprofen in a study of 400 mg 4-times daily is greater than the posology of the current product which has a maximum of 3 tablets (equivalent to 1200 mg total) daily. Another study showed ibuprofen to be inferior to etoricoxib. None of the studies included children or adolescents ≥12 and <15 years.
Additional studies were reported in a systematic review by another author.

Fifty-six randomised controlled trials describing 55 comparisons of analgesics with placebo and 12 direct comparisons with other analgesics were included. Ibuprofen, mefenamic acid and aspirin acid were superior to placebo but paracetamol was not. The requirement for rescue analgesics, restriction of daily life and absence from work or school were less frequent with naproxen and ibuprofen than placebo but not with aspirin or paracetamol. Direct comparisons did not show any difference between naproxen and ibuprofen. Side effects occurred more frequently only with naproxen when compared with placebo. Naproxen, ibuprofen, mefenamic acid and aspirin were all found to be effective in primary dysmenorrhoea. Ibuprofen appeared to have the most favourable risk-benefit ratio.

**Assessor comments**

Details of the ibuprofen preparations, dose and posology in the clinical studies reviewed are not clearly documented, and it is not apparent that any of the studies used ibuprofen lysine in particular.

However, several of the studies appear to have used ibuprofen dosing equivalent to the current product (400 mg ibuprofen), with data supporting a claim of superiority over placebo and comparability with other NSAIDs. Only one author appears to have included adolescents (>14 years) in the trial group, and so the data in the paediatric/adolescent population are very limited.

Ten individual studies were presented in support of the dysmenorrhoea indication.

**Assessor comments**

None of the studies reported appear to have studied ibuprofen lysine in particular. One study used ibuprofen arginine, a rapidly absorbed ibuprofen preparation similar to ibuprofen lysine, although this was an open label, non-comparative trial.

The studies by three authors studied doses of ibuprofen of 400 mg 4-times daily, greater than the posology of the current product. These studies do provide supportive efficacy data for ibuprofen in dysmenorrhoea.

Studies with comparative posology to the current product provide evidence of analgesic effect of ibuprofen superior to placebo and comparable to other NSAIDs. One author included patients over 15 years of age, and an open label study included patients over the age of 13 amongst its 838 subjects. It is, however, not clear from the evidence provided how many subjects have been studies in the paediatric/adolescent population at a comparable dose/posology of the current ibuprofen lysine 684 mg tablets.

**Conclusions on dysmenorrhoea:**

It is acknowledged that published clinical guidelines refer to the use of ibuprofen in dental pain, and other comparable products include this indication.

The MAH has provided limited data specifically regarding ibuprofen lysine in dysmenorrhoea. It is considered that sufficient evidence is provided to support the use of ibuprofen in the indication of dysmenorrhoea.

**Muscular pain**

Analgesics are commonly prescribed, or used without prescription, for acute soft tissue injuries. Traditional non-selective, non-steroidal anti-inflammatory drugs (NSAIDs) are the analgesic agents...
most often prescribed worldwide as they have both analgesic and anti-inflammatory effects. The rationale for use of NSAIDs for acute soft tissue injury is that pain and swelling are due to inflammation, so NSAIDs will improve symptoms because they reduce inflammation. Nonsteroidal anti-inflammatory drugs are the most commonly used medications in the treatment of myofascial pain. Although NSAIDs are devoid of any direct effect on skeletal muscle contraction, they are frequently used as a first-line treatment for conditions involving muscle pain.

The MAH refers to BMJ Best Practice guidelines recommending ibuprofen 200-400 mg orally every 4-6 hours (when required), with maximal daily dose of 2400 mg, as primary analgesic option for groin pain, a common presenting symptom for patients of widely varying ages in the primary care setting. Common causes include trauma and overuse injuries.

The Guideline from BMJ Best Practice recommends ibuprofen 400-600 mg orally every 4-6 hours (when required) as secondary analgesic option for musculoskeletal sprains and strains (BMJ Best Practice - musculoskeletal sprains and strains, 2017). Ibuprofen 300-400 mg orally every 6-8 hours (when required) is recommended as primary analgesic option in chronic pain due to musculoskeletal (mechanical) causes, neurological causes, psychological causes or localised disease, or as part of a generalised disease process (BMJ Best Practice - chronic pain syndromes, 2017).

A Cochrane review is presented, which included 16 trials of NSAIDs and other oral analgesics with a total of 2144 participants, predominantly young adults. Participants of seven trials had acute ankle sprains and in the other trials participants were treated for a variety of conditions; these were either solely or mainly soft tissue injuries. Four studies investigated the efficacy of ibuprofen in comparison with paracetamol only, or with combination of ibuprofen – paracetamol and codeine - paracetamol (see table below). The results from these studies reportedly showed better or comparable efficacy between ibuprofen and any comparator agents.

**Assessor comments**
None of the studies reported investigated the efficacy of ibuprofen lysine in muscular pain.

One study used a total daily dose greater than that recommended for the current product. Another study included patients from the age of 6 to 17 years, an age range younger than that indicated for the current product. However, this can be considered supporting data for ibuprofen for the adolescent population, given that results indicated superior clinical efficacy over codeine or paracetamol. One author studied a posology comparable to the current product, indicating similar efficacy to paracetamol for pain relief score in 260 adults with lateral ankle sprains.

The MAH cites 6 additional studies in muscular pain.

**Assessor comments**
None of the studies reported investigated the efficacy of ibuprofen lysine in muscular pain. Five of these six studies used ibuprofen dosing equivalent to the posology of the current product.

One study is supportive of superiority of ibuprofen over placebo, although the magnitude of the treatment effect is not reported. In lower limb soft tissue injuries, ibuprofen appears to be more efficacious than aspirin) in adults. Ibuprofen is reported to have similar efficacy to aspirin and to sulindac (NSAID) in musculoskeletal disease, although the spectrum of pathology for this study is not defined.

**Conclusions on muscular pain:**
Ibuprofen is widely used as to provide analgesia in painful musculo-skeletal conditions, and evidence is provided to demonstrate superiority over placebo.

UK National Institute for Care Excellence (NICE) recommends paracetamol for initial management of sprains and strains, on the basis that (i) there is no clinically important difference in efficacy between paracetamol and oral NSAIDs, but evidence of more gastrointestinal adverse effects with NSAIDs compared to paracetamol; and (ii) expert opinion in review articles on the management of sprains and strains is that oral NSAIDs should not be used in the first 48 hours after the initial injury because of concerns that they may delay healing. The NICE guidance states that oral NSAIDs should be considered 48 hours after the initial injury, if needed.

It is agreed that there is a consistent evidence of a lack of significant efficacy differences between NSAIDs such as ibuprofen and paracetamol in muscular pain. However, an increase in (particularly GI) AEs is of consideration, particularly if NSAIDs are considered for more chronic musculo-skeletal conditions such as fibromyalgia. For this OTC medicine, this can be mitigated by the instruction to seek medical advice from a doctor if symptoms persist.

It is considered that sufficient evidence is provided to support the use of ibuprofen in the indication of muscular pain.

**Back pain**

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medications worldwide and are widely used for patients with low-back pain. The rationale for the treatment of low-back pain with NSAIDs is based both on their analgesic potential and their anti-inflammatory action. 

The general approach to the treatment for acute non-specific low back pain by the Royal College of General Practitioners and the American Pain Society is advice to stay active and to avoid bed rest, plus pain relieving medications such as paracetamol, weak opioids or NSAIDs. Based on Guidelines for treatment of musculoskeletal lower back pain, NSAID analgesics are recommended as adjunct to the conventional treatment with ibuprofen being the primary option from the NSAIDs (BMJ Best Practice - musculoskeletal lower back pain, 2017; BMJ Best Practice - back pain, 2017).

**Assessor comments**

UK NICE guidance for the management of low back pain in over 16s recommends a range of interventions, including non-pharmacological, pharmacological and invasive options. For pharmacological treatments, the guidance is to consider oral NSAIDs for managing low back pain, taking into account potential differences in GI, liver, and cardio-renal toxicity, and patient’s risk factors. In addition, prescribers are advised to think about appropriate clinical assessment, ongoing monitoring of risk factors and the use of gastroprotective treatment. Per the SmPC, the NICE guidance states that the lowest effective dose for the shortest possible period of time should be used.

MAH refers to a Cochrane review for evidence in support of the indication for back pain.

**Assessor comments**

None of the studies reported here used ibuprofen lysine for treatment of back pain. The data provided is mixed evidence for ibuprofen in backpain.

Ibuprofen in combination with a muscle relaxant was preferred over ibuprofen alone for acute low back pain in adults. The SR ibuprofen product in one study is not comparable to the current rapid-onset formulation, and the dosing of ibuprofen in another study was twice the dose intended with the current product. Ibuprofen at a dosing higher than indicated for the current product was similar to nimesulide
Ibuprofen of comparable dosing to the current product was less effective than local heat therapy.

Ibuprofen 400 mg, equivalent to the dose in the current product, was superior to placebo on global assessment in acute low back pain in 369 adults. Studies with equivalent posology to the current product showed superior efficacy over diclofenac in a small study of 30 patients, and comparable efficacy to a felbinac (NSAID) preparation in 287 adults with acute low back pain.

No data are provided in these studies to support ibuprofen in the indication of back pain in children/adolescents ≥12 and <18 years.

One additional study is presented, for which the MAH states that the analgesic effect noted in subjects treated with a heating pad or cold pack in conjunction with ibuprofen was postulated to be the result of the ibuprofen therapy.

Assessor comments
The additional study does not provide clear evidence of efficacy of ibuprofen in support of the low back pain indication in the target population.

Conclusions on back pain:

It is acknowledged that oral analgesia in the form of NSAIDs for back pain is in line with evidence-based guidance, including the UK NICE Clinical Knowledge Summary and NICE guideline Low back pain and sciatica in over 16s: assessment and management.

The data provided does not unanimously support the use of ibuprofen in the treatment of low back pain, but several studies are reported to demonstrate superiority over placebo and comparability with other NSAIDs. It is noted that NSAIDs including ibuprofen are recommended as analgesia for low back pain in patients over 16 years old, whereas paracetamol, for example, is not recommended.

It is considered that sufficient evidence is provided to support the use of ibuprofen in the indication of back pain.

Rheumatic pain

Several pharmacologic options are available for patients with rheumatoid arthritis. The MAH states that the general approach for pharmacologic treatment of rheumatic pain is using NSAIDs as medicines of first level. They refer to BMJ Best Practice Guidelines for rheumatoid arthritis and chronic pain syndromes, stating that NSAIDs are recommended as adjunct therapy and ibuprofen, as part of this group, is recommended as primary treatment option for treatment of rheumatic pain.

Assessor comments
The current UK NICE guidance states that for patients (>16 years) with suspected rheumatoid arthritis, NSAIDs such as ibuprofen should be used if pain is not controlled following a trial of paracetamol with or without codeine for pain relief, with the lowest effective dose for the shortest period of time. For patients with established RA, NICE recommends the immediate symptom control of a RA flare be a NSAID plus paracetamol ± codeine, whilst awaiting specialist advice. UK clinical guidelines are therefore consistent with a role for ibuprofen in adults with suspected or established RA as adjunctive treatment. In osteoarthritis, oral NSAIDs are suggested if paracetamol and/or topical NSAIDs are ineffective.
A review of RCTs is cited, which includes one study, comparing ibuprofen at either 2400 mg or 1200 mg with paracetamol 4000 mg for analgesia in 184 patients with chronic knee pain from OA. All three groups had improvement in outcome variables with no significant difference between groups.

**Assessor comments**
None of these studies evaluated the role of ibuprofen lysine in rheumatic pain.

In one study, the 1200 mg dosing is consistent with the posology of the current product and was equivalent to maximum daily dose of paracetamol in adults with OA.

The additional cited study is 50 years old, and the ibuprofen dose is not in line with the dosing of the current product.

An additional 15 studies are cited in support of the indication for rheumatic pain.

**Assessor comments**
None of the cited studies evaluated ibuprofen lysine in rheumatic pain.

Of these 15 additional studies, 8 appear to have studied ibuprofen with a comparable posology to the current product. Study details are limited, but these data are supportive for ibuprofen as superior to placebo in OA and inflammatory polyarthritis, superior to paracetamol in lower limb OA, comparable to other NSAIDs in RA and OA and comparable to glucosamine in OA.

Tolerability of ibuprofen was reportedly comparable to aspirin and paracetamol in a large randomised, blinded study of 4342 patients with different musculoskeletal conditions. Further details on this study, such as dose/posology, range of pathology, rates/nature of AEs are not provided in the narrative supplied.

**Conclusions on rheumatic pain**

The role of NSAIDs such as ibuprofen as an option for analgesia in rheumatic pain from conditions such as RA and OA is acknowledged, and is included in evidence-based clinical guidelines. Several studies have been cited that provide supportive evidence for ibuprofen as superior to placebo and comparability to other analgesic options such as paracetamol and other NSAIDs in different rheumatic conditions in adults.

It is considered that sufficient evidence is provided to support the use of ibuprofen in the indication of rheumatic pain.

**Fever; symptoms of cold and influenza**

Common cold and flu are the most common human illnesses; characterised by upper and lower respiratory tract symptoms of rhinorrhoea, cough, fever, chills, headache, and myalgia. Fever in a child is one of the most common clinical symptoms managed by paediatricians and other health care providers and a frequent cause of parental concern. Over-the-counter (OTC) analgesics, especially NSAIDs have been widely used for the treatment of pain and fever associated with the common cold. NSAIDs, e.g. aspirin, ibuprofen and naproxen, have analgesic (pain reducing), antipyretic (fever reducing) and, in higher doses, anti-inflammatory effects.
The MAH cites the Italian National Guidelines System recommending paracetamol and ibuprofen in the treatment of fever and pain in children, and that paracetamol, ibuprofen and diclofenac can be used, if needed, for the treatment of fever and pain in adults. The BMJ Best Practice Guidelines for common cold and influenza are also cited, recommending ibuprofen as primary treatment option in adults and children.

**Assessor comments**

UK NICE clinical knowledge summaries recommend the use of NSAIDs such as ibuprofen for symptomatic relief in both adults and children with common cold or seasonal influenza.

MAH cites a Cochrane review, which includes 5 studies using ibuprofen in common colds, with duration of treatment for up to 7 days.

**Assessor comments**

None of the studies investigated ibuprofen lysine in particular for symptom relief. Only two of the studies reported in the cited Cochrane review had dosing/posology comparable to the current product. Detailed results are not provided, but the summaries are supportive for a role for ibuprofen for symptom relief in adults with common cold.

An additional review article by is discussed that is not reported in the summary table of the Clinical Overview. It is reported that this review identified 8 RCTs investigating the effect of paracetamol and ibuprofen on children with fever. Comparing temperature differences at time-points between 1 and 6 hours after dosing, statistical meta-analysis showed that there was no clear benefit for one drug over the other, but a small superior effect at temperature lowering was evident for ibuprofen over paracetamol at 6 hours. Both medicines were well tolerated, and no differences in AEs reported.

A further 20 individual studies evaluating efficacy of ibuprofen for treatment of symptoms of common cold and influenza were submitted.

**Assessor comments**

Of the twenty additional studies provided, none of the studies specifically investigated ibuprofen lysine for its efficacy in symptomatic relief in cold and influenza.

The study details provided were limited, and at least 14 of the studies were conducted in children younger than the indicated population of the current product, and used oral suspension preparations. Nonetheless, these trials do provide extensive supportive data for ibuprofen as an antipyretic in children with febrile conditions.

With dosing lower than that of the current product, one author reported superiority of ibuprofen over placebo and comparability with diclofenac for symptomatic relief of fever, headache, muscular ache and joint pains in adults with influenza-like conditions.

The only cited study with comparable posology to the current product reportedly showed that ibuprofen was more effective than paracetamol for symptomatic relief of pain on odynophagia and dysphagia. The demographics of the 113 patients is not specified. Three of the studies investigated intravenous ibuprofen for reduction of fever in adults, reporting superior efficacy over placebo and paracetamol.

**Conclusions on cold and flu**

NSAIDs such as ibuprofen are recommended for treatment of cold and influenza symptoms in both adults and children in evidence based clinical guidelines.
The data provided is limited in scope, with relatively few studies provided that have a comparable posology to the current product, although the studies provided do provide some supportive data for superiority of ibuprofen formulations over placebo and comparability to paracetamol/other NSAIDs in the cold/flu indication. It is considered that sufficient evidence is provided to support the use of ibuprofen in the indication of fever and symptoms of cold and flu in adults.

**Posology**

Self-medication is the treatment of choice for pain, especially for mild to moderate acute pain and most patients use over-the-counter drugs. Because of its favourable safety profile, a 200 mg and 400 mg formulation of ibuprofen and ibuprofen 100 mg/5 ml oral suspension, with a maximum recommended daily dose of 1200 mg ibuprofen) was approved as an OTC analgesic in the UK in 1983, followed by a similar USA approval one year later. Its efficacy and safety in relieving mild to moderate pain are well-documented and have been demonstrated in numerous randomized, double blind clinical studies.

Ibuprofen 400 mg has been shown to be as effective as aspirin 600 or 900 mg/day in models of moderate pain but superior to aspirin or paracetamol in more sensitive models such as dental pain. The duration of action of ibuprofen 400 mg is at least 6 hours compared with 4− 6 hours for ibuprofen 200 mg. Maximal daily dose should not exceed 1200 mg, in accordance with recommendations for the OTC use of ibuprofen for the management of acute pain and fever.

Consequent to the proposed extension of the indications for this product, the MAH proposes to amend the duration of treatment (section 4.2 of SmPC). The current approved duration of use for this OTC product is 3 days, which the MAH states is a reflection of its use limited to treatment of headache and migraine. The proposed updated posology is:

“If in children and adolescents between 12 and 18 years this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

For adults, the patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 5 days when treating pain and 3 days when treating migraine or fever.”

The MAH states that for the reference product and its EU licenses, the advice regarding duration of treatment is not harmonised, and MAH has provided the following table of duration of treatment recommendations in several MS:

<table>
<thead>
<tr>
<th>Country</th>
<th>Product name, MAH, date of first authorisation</th>
<th>Active substance</th>
<th>Ph. Form</th>
<th>Strength</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>Nurofen Express 684 mg Caplets, Reckitt Benckiser Healthcare (UK) Ltd, 17/01/2006, MA No. PL 00063/0384</td>
<td>ibuprofen lysine</td>
<td>film-coated tablets</td>
<td>400 mg</td>
<td>Adolescents – 3 days, Adults – 10 days (SmPC Nurofen Express 684 mg Caplets, 2017)</td>
</tr>
<tr>
<td>BE</td>
<td>NUROFEN 400 FASTTABS 400 mg, comprimes pellicules, Reckitt Benckiser Healthcare (Belgium), 12/07/2002, MA No: BE228551</td>
<td>ibuprofen lysine</td>
<td>film-coated tablets</td>
<td>400 mg</td>
<td>Adolescents – 3 days, Adults - 3 days in case of fever or 4 days for the treatment of pain (SmPC NUROFEN 400 FASTTABS, 2015)</td>
</tr>
<tr>
<td>AT</td>
<td>Nurofen rapid 400 mg - Filmtabletten, Reckitt Benckiser Deutschland GmbH, 15.09.2000, MA No. Z. Nr.: 1-23773</td>
<td>ibuprofen lysine</td>
<td>film-coated tablets</td>
<td>400 mg</td>
<td>Adolescents – 3 days, Adults - 3 days in case of fever or 4 days for the treatment of pain (SmPC Nurofen rapid, 2010)</td>
</tr>
<tr>
<td>FR</td>
<td>NUROFENFLASH 400 mg</td>
<td>ibuprofen film-</td>
<td>400 mg</td>
<td>Adolescents – 3 days</td>
<td></td>
</tr>
</tbody>
</table>
Assessor comments

RMS acknowledges that the duration of treatment for ibuprofen is not harmonised across EU Member States. Of the MS in the table provided by the MAH, only Poland is a CMS in this procedure.

The proposed duration of treatment is consistent with another ibuprofen (not lysine) product approved to the MAH of the current product (Ibuprofen 400 mg film-coated tablets; PL 34088/0039, UK/H/5480/001/002/DC).

The proposed duration of treatment in adults is more conservative than the current authorised duration for the UK reference product (Nurofen Express 684 mg PL 00063/0384), for which adult patients may take the product for up to 10 days. It is acknowledged that other comparable ibuprofen lysine products in the UK, with a broader indication than the UK reference product similar to that proposed for the current case, state that adult patients should consult a doctor if the product is required for more than 4 days for pain or 3 days for fever.

The conditions for supply of ibuprofen lysine as ‘P’ (OTC supply through pharmacies only) in UK state that for approved indications (including rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.), the patient should consult a doctor if symptoms persist or worsen or if the product is required for more than 10 days.

The proposed duration of treatment for children/adolescents (3 days) is in line with the UK reference product, comparable products in the UK and other MS, and is agreed.

Considering that (i) the current product is a European authorised product and not solely for national use in the UK, and (ii) that the proposed wording for treatment duration is more conservative than UK national requirements, the proposal is acceptable.

III.3.3 Clinical safety

No new data relating to clinical safety has been provided.

Risk Management System

The MAH has submitted a Risk Management System.
**Assessor comments**
The application states that the RMP has been updated, and the reasons for update have not been provided. It is assumed that the update relates to the revised SmPC. The RMP version was approved in January 2018, through the initial MA application. The summary table of safety concerns are unchanged and acceptable; however, the applicant is advised that the RMP should now be constructed in line with GVP module V rev 2. The revised RMP template removes the need to include a copy of SmPC. This removes the need to update the RMP with every regulatory change to the SmPC unless an important risk is identified. The revised RMP structure is mandatory after 31 March 2018.

### III.2 Product information

Consequent to the proposed SmPC changes, the applicant has submitted updated versions of the patient leaflet and label to reflect the agreed SmPC amendments.

#### III.4.1 Summary of Product Characteristics

Refer to assessment of Clinical Efficacy and Safety, as above.

#### III.4.2 Package leaflet and user test

**Assessor comments**
The wording of the patient leaflet has been updated to reflect the agreed amendments to the SmPC.

#### III.4.3 Labelling

**Assessor comments**
The wording of the labelling has been updated to reflect the agreed amendments to the SmPC.

### IV. Assessment of the responses to the Member State(s) Request for supplementary information

**Request for supplementary information as proposed by the RMS (UK)**

**Product information**

**SmPC**
The wording of the SmPC has been updated to reflect the agreed amendments.

**Patient leaflet and labelling**
The wording of the patient leaflet and labelling have been updated to reflect the agreed amendments to the SmPC.
Assessment of the MAH’s response

The editorial changes requested by RMS UK have been implemented as suggested. This is accepted.

The proposed duration of treatment prior to consulting a doctor in adults is more conservative than the current authorised duration for the UK reference product (Nurofen Express 684 mg PL 00063/0384), for which adult patients may take the product for up to 10 days. The conditions for supply of ibuprofen lysine as ‘P’ (OTC supply through pharmacies only) in UK state that for approved indications (including rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhea, feverishness, symptoms of colds and influenza.), the patient should consult a doctor if symptoms persist or worsen or if the product is required for more than 10 days. Considering that (i) the current product is a European authorised product and not solely for national use in the UK, and (ii) that the proposed wording for treatment duration is more conservative than UK national requirements, the MAH’s proposal is considered acceptable.

Risk Management Plan

- When updating the RMP, the Applicant should take into account the 2nd revision of the RMP template (available at the link below, published on the EMA website on 30th March 2017), which becomes mandatory as of 31st March 2018.


Applicant’s response:

We acknowledge and agree the Agency comment, therefore an updated RMP Version is prepared. The RMP was prepared in line with GVP module V rev 2 and its update was made in relation to the revised SmPC.

Assessment of the MAH’s response

Table VIII.1: Summary of safety concerns

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
<td>Gastrointestinal (GI) bleeding, ulceration and perforations</td>
<td>Impaired fertility</td>
<td>Breast feeding</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular and cerebrovascular events (hypertension, heart failure, arterial thrombotic events)</td>
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<td></td>
<td>Hypersensitivity</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Hepatic and renal disorders</td>
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<td></td>
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<td></td>
<td>Use during pregnancy (including risk of premature closure of ductus arteriosus)</td>
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<td></td>
<td>Severe skin reactions (Stevens-Johnson syndrome, epidermal necrosis)</td>
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<tr>
<td></td>
<td>Interaction with anti-coagulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interaction with anti-hypertensives</td>
<td></td>
<td></td>
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</tbody>
</table>
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended. There are no differences from other products containing this active in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety. In line with other products containing this active, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

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 Competent Authority;
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.

The MAH has submitted an updated RMP in line with GVP module V rev2. The main body of this public assessment report section IV.6 has been updated to reflect this.

**CMS comments (CZ)**

**Product information**

**Patient leaflet (Section 1):**

Please be aware that the indication “rheumatic pain” is considered unacceptable for self-treatment. The following text is required to be amended in this section: “For rheumatic pain, the product must be used only upon a doctor’s recommendation.”

**Applicant’s response:**

We acknowledge the Agency comment and agree to add the suggested wording regarding rheumatic pain in the Patient Leaflet. The amended Patient Leaflet is presented in Module 1, Section 1.3.1 SPC, Package Leaflet and Labelling – common.

**RMS Assessment of the MAH’s response**

The MAH has updated Section 1 of the PIL to incorporate the suggested wording of the CMS (CZ).

The RMS considers that this proposed additional wording is not appropriate for a product that is available without prescription in some Member States, and should be deleted.

**Conclusion – point not resolved**

**Labelling (Section 15):**

Only those indications for self-treatment should be listed here. The indication “rheumatic pain” thus should be deleted (please see the comment on PL Section 1).
Applicant’s response:

We acknowledge the Agency comment and agree to remove the indication rheumatic pain from the Labelling. The amended Labelling is presented in Module 1, *Section 1.3.1 SPC, Package Leaflet and Labelling – common*. The amended mock-up of the box is presented in Module 1, *Section 1.3.2 Mockup – common*.

**RMS Assessment of the MAH’s response**

The MAH has updated Section 15 of the labelling to remove the indication of “rheumatic pain”.

RMS considers that the deletion of the indication of rheumatic pain from the package labelling is not appropriate when the indication is stated in the SmPC and PIL. The labelling and PIL should be an accurate representation of the clinical indications listed in section 4.1 of the SmPC.

If the MAH proposes to delete the wording from the package labelling, the indication must also be removed from the SmPC and PIL for consistency of information in the product information.

*Conclusion – point not resolved (see Section VI)*

**V. Request for supplementary information as proposed by the RMS**

**VI. Assessment of the responses to the Member States Request for supplementary information**

The MAH has provided additional responses to the further request for supplementary information and comments raised by CMS-CZ regarding the product information.

*Patient leaflet (Section 1)*

**RMS (UK) comment**

The MAH has updated Section 1 of the PIL to incorporate the suggested wording of the CMS (CZ).

The RMS considers that this proposed additional wording is not appropriate for a product that is available without prescription in some Member States, and should be deleted.

**CMS (CZ) comment**

Generally, the indication “rheumatic pain” is approved in many analgesics, and according to RMS assessment, the efficacy in this indication has also been demonstrated in this medicinal product. All approved indications are then listed in SmPC, as well as in the PL, to maintain the consistency. Nevertheless, in our long-term routine practice applied to non-prescription products, the indication “rheumatic pain” is considered unacceptable for self-treatment. Therefore, all non-prescription products authorized in the CZ with this indication in SmPC have the warning in PL, that the product must be used only upon a doctor’s recommendation. Such warning in PL does not cause the inconsistency with SmPC since all indications provided in SmPC Section 4.1 are listed in PL Section 1. Nevertheless, CZ is aware that for some CMS, the indication “rheumatic pain” is acceptable for self-treatment, and therefore we propose to amend this warning to CZ PL only as a blue-box.
Labelling (Section 15)

RMS (UK) comment

The MAH has updated Section 15 of the labelling to remove the indication of “rheumatic pain”.

RMS considers that the deletion of the indication of rheumatic pain from the package labelling is not appropriate when the indication is stated in the SmPC and PIL. The labelling and PIL should be an accurate representation of the clinical indications listed in section 4.1 of the SmPC.

If the MAH proposes to delete the wording from the package labelling, the indication must also be removed from the SmPC and PIL for consistency of information in the product information.

CMS (CZ) comment

We do not endorse RMS opinion that there would be inconsistency of information between SmPC/PL and labelling in case the indication is removed from labelling. In our opinion, RMS request is not substantiated, since the efficacy in this indication has been demonstrated. Please be aware that it is our long-term routine practice to provide only those indications for self-treatment on the labelling. This enables the patients to consider whether this product is intended for their disease/condition or not. Secondly, the pack sizes of non-prescription products are usually small and there is usually not enough space to provide all approved indications. We therefore propose to modify the CZ labelling only as a blue-box (in terms that the indication “rheumatic pain” is not listed in CZ labelling).

Applicant’s response:

We acknowledge the RMS Assessment and the CMS-CZ comment. Since safety and efficacy of ibuprofen in the indication "rheumatic pain" has been established we propose to keep this indication in the SmPC, PIL and Labelling.

In order to comply with the RMS position and maintain consistency between the SmPC, PIL and Labelling, and additionally comply with the national practice of use of non-prescription products in the CMS-CZ, we have highlighted the changes in the PIL and Labelling that will be appropriately implemented on national level in CMS-CZ, as per CZ national blue-box requirement. The amended PIL and Labelling are presented in Module 1, Section 1.3.1 SPC, Package Leaflet and Labelling – common.

RMS Assessment of the MAH’s response

The MAH has amended the PIL and Labelling, as requested by RMS in the previously circulated FVAR.

- Leaflet – the additional wording relating to the use of the product for rheumatic pain only upon doctor’s recommendation has been deleted, as requested by RMS. The aforementioned text is highlighted on the PIL as text to be implemented on a national level by CMS-CZ.
- Labelling – the full list of indications stated in SmPC section 4.1 (as per the conclusion of this variation procedure) is now correspondingly represented on the labelling, as requested by RMS. The indication of ‘rheumatic pain’ is highlighted on the labelling as text to be modified on a national level by CMS-CZ.

Regarding the above, CMS-CZ has provided the following statement:
Please be informed that CZ fully endorses the Applicant’s responses, PL and labelling are acceptable and CZ agrees that the highlighted changes will be appropriately implemented on national level to CZ PL and CZ labelling.

Conclusion – issue resolved.

VII. UPDATED OVERALL CONCLUSION

This product was recently approved after a Decentralised Procedure in which the product information, including approved indications, was aligned with the chosen reference product. This variation procedure seeks to widen the approved indication, and MAH has provided both regulatory and scientific justifications.

A regulatory justification simply based upon a broader range of indications in CMSs than the RMS is considered unacceptable per se, as the legal basis of the application under 10(1) requires alignment with the Reference product, which in this case is the UK version of Nurofen Express PL 00063/0384.

The widespread use of related ibuprofen and ibuprofen lysine products for a range of indications is acknowledged, as are the evidence-based clinical guidelines that indicate a role for ibuprofen in the proposed additional clinical indications. For the addition of new indications to section 4.1 of the SmPC, provision of clinical data is to be expected and, in lieu of new clinical trials with the current product, references to published literature can be acceptable. It is acknowledged that the pharmacodynamic effects of ibuprofen lysine are mediated by ibuprofen and the MAH has provided a considerable body of literature in support of the efficacy of ibuprofen in each of the proposed additional indications. Although specific references pertaining to the use of ibuprofen lysine in these indications and studies relating to the adolescent population are very limited, it is considered that the references supplied are sufficient overall to support a role for ibuprofen in all these additional indications.

The lack of harmonisation of SmPC for ibuprofen/ibuprofen lysine salts across Europe is acknowledged. As the national Marketing Authorizations of the reference products fall under the scope of the same Global Marketing Authorisation (MAH-Reckitt Benckiser), and the broader range of indications for the RP is accepted in other MSs, the proposal to widen the indication for the current product, in this case, can be considered acceptable. The proposal is in line with UK MHRA guidance for the active substance of ibuprofen lysine for the non-prescription/‘OTC’ classification. Acceptable responses have been received to the further request for supplementary information regarding the patient information leaflet and labelling (Section VI, above), and differences in product information (leaflet and labelling) will be implemented on a national level by the respective CMS.

There are no outstanding issues, and the application can be accepted.

Approved on 04/10/2018.