Public Assessment Report

Decentralised Procedure

Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension

Procedure No: UK/H/5545/001/DC

UK Licence No: PL 14598/0103

Boehringer Ingelheim International GmbH
Lay Summary

Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension
(ibuprofen and pseudoephedrine hydrochloride)

This is a summary of the public assessment report (PAR) for Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension (PL 14598/0103; UK/H/5545/001/DC). It explains how Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension.

For practical information about using Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension, patients should read the patient information leaflet (PIL) or contact their doctor or pharmacist.

What is Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension and what is it used for?
Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension is a medicine with ‘well-established use’. This means that the medicinal use of the active substances of Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension, both individually and in combination, have been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension is effective in the relief of feverishness and symptoms of colds and influenza with associated congestion, including aches and pains, headache, sore throat, blocked nose and sinuses for adults and adolescents aged 15 years and above.

How does Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension work?
Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension contains the active substances ibuprofen and pseudoephedrine hydrochloride. Ibuprofen belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs provide relief by changing the body's response to pain, swelling and high temperature. Pseudoephedrine belongs to a group of drugs called vasoconstrictors, which act on the blood vessels in the nose to relieve nasal congestion.

How is Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension used?
Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension should be taken by mouth.

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

Depending on the severity of the symptoms, the recommended dose is 10 to 20 ml every six
hours. The medicine should be used for the shortest time possible and at the lowest dose to relieve the symptoms. The maximum daily dose of 60 ml should not be exceeded. The medicine should not be given to children under 15 years of age.

This combination product should only be taken if the patient has a blocked nose with pain or fever. If they have only one of these symptoms they should talk to their pharmacist or doctor about using mono preparations alone.

Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension can be obtained without a prescription.

**What benefits of Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension have been shown in studies?**

As ibuprofen and pseudoephedrine hydrochloride are well-known substances, and their combined use in the effective relief of feverishness and symptoms of cold and influenza with associated congestion, including aches and pains, headache, sore throat, blocked nose and sinuses is well-established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the combined use of ibuprofen and pseudoephedrine hydrochloride in the effective relief of symptoms of the common cold and influenza with associated congestion.

In addition, a bioequivalence study was conducted to show that the combination of the active ingredients in a single product was comparable to administration of these active ingredients in separate products. Medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects from Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension?**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

For information about side effects that may occur with using Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension, please refer to the PIL or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**Why is Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension approved?**

The use of ibuprofen and pseudoephedrine hydrochloride, in combination, for the effective relief of symptoms of the common cold is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension outweigh the risks and the grant of the marketing authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension?**

A risk management plan has been developed to ensure that Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for this product,
including the appropriate precautions to be followed by healthcare professionals and patients.

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

**Other information about Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension**

Germany and the UK agreed to grant a marketing authorisation for Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension on 21 August 2014. The marketing authorisation in the UK was granted on 23 September 2014 to Pharos – Pharmaceutical Oriented Services Ltd (PL 23022/0111).

The MA Holder in the UK subsequently underwent a change of ownership procedure to the current MA Holder, Boehringer Ingelheim International GmbH, on 04 December 2014 (PL 14598/0103).

The full PAR for Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension follows this summary.

For more information about treatment with Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension, read the PIL or contact your doctor or pharmacist.

This summary was last updated in December 2016.
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I Introduction

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation (MA) to PharOS-Pharmaceutical Oriented Services Ltd for the medicinal product Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension. This pharmacy (P) medicine is indicated for the relief of feverishness and symptoms of colds and influenza with associated congestion, including aches and pains, headache, sore throat, blocked nose and sinuses.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Germany as a Concerned Member State (CMS). This application was made under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use.

The medicinal product contains the active substances ibuprofen and pseudoephedrine hydrochloride.

Ibuprofen is a propionic acid derivative, having analgesic, anti-inflammatory and antipyretic activity. The drug’s therapeutic effects as a non-steroidal anti-inflammatory drug are thought to result from inhibitory activity on an enzyme known as cyclooxygenase (COX), which is responsible for prostaglandin synthesis. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Pseudoephedrine, like ephedrine, is a sympathomimetic drug that is a direct, non-selective activator of α-adrenergic receptors and, to a lesser degree, of β1- and β2-adrenergic receptors. Additional to these actions, pseudoephedrine provides a relatively short-term presynaptic effect on noradrenergic neuron terminals, thereby causing the release of noradrenaline. Activation of α-adrenergic receptors inhibits adenylate cyclase, which in turn stops producing cyclic 3′,5′-adenosine monophosphate. The sympathomimetic effect of pseudoephedrine produces vasoconstriction, which in turn relieves nasal congestion.

With the exception of one bioavailability study, cited from the scientific literature, no new non-clinical or clinical studies were conducted for this application, which is acceptable given this is a bibliographic application for a product containing active substances of well-established use.

Bioavailability study results were submitted supporting the application to show that the combination of the active ingredients in the proposed product (100 mg/5ml ibuprofen and 15 mg/5ml pseudoephedrine hydrochloride) is comparable to administration of these active ingredients in separate products: Orbifen For Children suspension (100 mg/5ml ibuprofen oral suspension) and Pseudoephedrine Hydrochloride Suspension (15 mg/5ml pseudoephedrine hydrochloride oral suspension). The study was conducted in accordance with Good Clinical Practice (GCP).

The efficacy of the actives and combination are well-established. An adequate discussion of the efficacy of pseudoephedrine and the combination has been provided. Further discussion of the efficacy of ibuprofen, pseudoephedrine and the combination has been provided in the course of the procedure by the applicant which is considered adequate to support the application.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MA holder has provided a Risk Management Plan (RMP).

The MA holder has provided a satisfactory Environmental Risk Assessment (ERA).

The RMS and CMSs considered that the application could be approved at the end of procedure (Day 210) on 21 August 2014. After a subsequent national phase, a licence was granted in the UK on 23 September 2014.

On 04 December 2014, the MA Holder in the UK, Pharos – Pharmaceutical Oriented Services Ltd (PL 23022/0111), underwent a change of ownership to the current MA Holder, Boehringer Ingelheim International GmbH (PL 14598/0103).
II Quality aspects

II.1 Introduction
The provided dossier for this application refers to a similar fixed-dose combination product, Orbifen cold & flu oral suspension (PL 17862/0004), which was submitted under Article 10a of Directive 2001/83/EC and authorised in the UK to Orbis Consumer Products Limited in 2007.

The product is formulated as a sugar-free, white, oral suspension with cherry flavouring, containing the active substances ibuprofen and pseudoephedrine hydrochloride at strengths of 100 mg/5 ml and 15 mg/5 ml, respectively. The excipients present are glycerol, xanthan gum, maltitol liquid, polysorbate 80, saccharin sodium, citric acid monohydrate, sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), cherry flavour (K11181) (consisting of: propylene glycol, water, flavouring substances and flavouring preparations, trisodium citrate buffer) and purified water.

The oral suspension is presented in a 100 ml amber Type III glass bottle with a child-resistant, tamper-evident, high-density polyethylene/polypropylene cap, with a polyethylene lining. The presentation includes a double-ended 5ml and 2.5ml polypropylene spoon to help measure the dose.

II.2 Drug Substance

Ibuprofen

INN: Ibuprofen
Chemical Name: \( \alpha \)-methyl-1-4-(2-methylpropyl)-benzeneacetic acid; p-Isobutylhydrotropic acid; 2-(4-Isobutylphenyl) propionic acid

Structure:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{H} & \quad \text{CO}_2\text{H} \\
\text{CH}_3 & \quad \text{and enantiomer}
\end{align*}
\]

Molecular formula: \( \text{C}_{13}\text{H}_{18}\text{O}_2 \)
Molecular weight: 206.28
Appearance: White or almost white, crystalline powder or colourless crystals.
Solubility: Practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

Ibuprofen is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, ibuprofen, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.
**Pseudoephedrine hydrochloride**

INN: Pseudoephedrine hydrochloride  
Chemical Name: (+)-(1S,2S)-2-Methylamino-1-phenylpropan-1-ol hydrochloride; d-Ψ-Ephedrine hydrochloride; d-isopseudoephedrine hydrochloride

Structure:

![Structure of Pseudoephedrine Hydrochloride](image)

Molecular formula: C_{10}H_{15}NO\cdot\text{HCl}
Molecular weight: 201.7
Appearance: White or almost white, crystalline powder or colourless crystals.
Solubility: Freely soluble in water and in ethanol (96 per cent), sparingly soluble in methylene chloride.

Pseudoephedrine hydrochloride is the subject of a European Pharmacopoeia monograph.

With the exception of some additional in-house tests undertaken by the substance manufacturer, all aspects of the manufacture and control of the active substance, pseudoephedrine hydrochloride, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

### II.3 Medicinal Product

**Pharmaceutical development**

The effects on the physical nature and stability of ibuprofen suspension in the presence of pseudoephedrine hydrochloride were analysed by comparing the dissolution profiles of the two oral suspensions: Orbifen For Children (containing 100mg per 5ml ibuprofen) and Orbifen cold & flu oral suspension (containing 100mg per 5ml ibuprofen and 15mg per 5ml pseudoephedrine). Similarity in the dissolution profiles was demonstrated by $f_2$ values of above 50 at all the three time points for all three pH levels. These results indicated that addition of pseudoephedrine hydrochloride does not affect the dissolution of ibuprofen, also suggesting similar *in-vivo* bioavailability.

All the excipients used in the manufacture of the proposed formulation, other than the cherry flavouring agent, comply with their respective European Pharmacopoeial monographs. The cherry flavouring agent complies with a satisfactory in-house specification.

Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients used contain material of animal or human origin.

**Manufacture of the product**

A satisfactory batch formula has been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot scale batches and a validation protocol reflecting the full scale batch is provided and is satisfactory.
Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided from three pilot-scale batches that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months with special storage conditions of “Do not store above 25ºC. Store in the original container in order to protect from light”.

In-use stability testing undertaken on two pilot scale batches of the finished product support a shelf life, after first opening, of 3 months.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III Non-clinical aspects
No new non-clinical data have been submitted and none are required for an application of this type. The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory.

The Environmental Risk Assessment (ERA) does not suggest that use of this product will pose a risk to the environment. It was agreed that a formal full ERA would not be necessary as the applicant has presented suitable information to justify the absence of significant increase of the environmental exposure due to ibuprofen and pseudoephedrine hydrochloride.

IV Clinical aspects
IV.1 Introduction
With the exception of one bioavailability study, no new clinical data have been submitted and none are required for an application of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
The applicant has included a bibliographic review of the pharmacokinetics of both active substances. It is not expected that the actives will interact pharmacokinetically with each other and the applicant has provided data from a study to demonstrate this.

Bioavailability study details were submitted supporting the application to show that the combination of active ingredients in the test product (100 mg/5ml ibuprofen and 15 mg/5ml pseudoephedrine hydrochloride) is comparable to administration of these active ingredients in the separate reference products (Orbifen For Children 100 mg/5ml ibuprofen oral suspension and Pseudoephedrine Hydrochloride 15 mg/5ml oral suspension).
An open-label, balanced, randomised, three-treatment, three-period, six-sequence, single-dose, crossover, comparative, oral bioavailability study was conducted in healthy, adult, male volunteers under fasting conditions.

A single oral dose of 10 ml of the suspension was administered following the treatment sequence as per the randomisation schedule. Blood samples were taken pre-dosing and up to 36 hours following administration. In treatment with Orbifen For Children Suspension, samples were only taken for up to 12 hours post dose. A washout period of 12 days was maintained between the periods.

The main pharmacokinetic results are presented below:

### In-transformed Least Square Means and Ratios for Ibuprofen with Confidence Interval

<table>
<thead>
<tr>
<th>End Point (Unit)</th>
<th>Mean Test (C)</th>
<th>Mean Reference (A)</th>
<th>Lower 90% C.I</th>
<th>Ratio</th>
<th>Upper 90% C.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (mcg/mL)</td>
<td>16.955</td>
<td>18.116</td>
<td>81.03</td>
<td>93.6</td>
<td>108.10</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (mcg.h/mL)</td>
<td>57.268</td>
<td>60.368</td>
<td>91.48</td>
<td>94.9</td>
<td>98.37</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (mcg.h/mL)</td>
<td>60.042</td>
<td>63.430</td>
<td>91.57</td>
<td>94.7</td>
<td>97.85</td>
</tr>
</tbody>
</table>

### In-transformed Least Square Means and Ratios for Pseudoephedrine Hydrochloride with Confidence Interval

<table>
<thead>
<tr>
<th>End Point (Unit)</th>
<th>Mean Test (C)</th>
<th>Mean Reference (B)</th>
<th>Lower 90% C.I</th>
<th>Ratio</th>
<th>Upper 90% C.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>97.836</td>
<td>98.451</td>
<td>92.41</td>
<td>99.4</td>
<td>106.87</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng.h/mL)</td>
<td>897.888</td>
<td>862.258</td>
<td>97.66</td>
<td>104.1</td>
<td>111.03</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng.h/mL)</td>
<td>927.278</td>
<td>888.184</td>
<td>97.94</td>
<td>104.4</td>
<td>111.28</td>
</tr>
</tbody>
</table>

The 90% confidence intervals of the geometric mean ratios for $AUC_{0-\infty}$ and $C_{max}$ for both ibuprofen and pseudoephedrine are within the 80.00%-125.00% range.

This shows that the combination of actives within the test product has equivalent bioavailability to the separate actives within the reference products.

### IV.3 Pharmacodynamics

The applicant has included a bibliographic review of the pharmacodynamics of both active substances. As the use of the actives is well-established, this is satisfactory.

### IV.4 Clinical efficacy

The applicant has included a bibliographic review of the pharmacodynamics of both active substances. As the use of the actives is well-established, this is satisfactory.

### IV.5 Clinical safety

The applicant’s safety summary for the actives and their combination is acceptable.

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

The applicant has submitted an 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 Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension. The safety profiles of ibuprofen and pseudoephedrine are well-established following decades of widespread use. No new risks have been identified for this combination product that are not recognised for the two individual active substances. Routine pharmacovigilance activities and risk minimisation measures should be adequate for this product, which contains two previously extensively used active substances with well-established safety profiles.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
### Important identified risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
<th>Preventability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Taking together a particular type of medicines used for depression, which are called monoamine oxidase inhibitors (MAOIs), such as phenelzine</strong></td>
<td>Medicines containing pseudoephedrine should not be taken with MAOIs currently or in the last two weeks, as they can react together and can increase blood pressure to very dangerous levels.</td>
<td>MAOIs must not be taken together with ibuprofen/pseudoephedrine hydrochloride, and treatment must be stopped at least 14 days before taking this medicine.</td>
</tr>
<tr>
<td><strong>Difficulty in passing into urine especially in patients with an enlarged prostate</strong></td>
<td>Pseudoephedrine acts on muscles and blood vessels by contracting them. In the prostate, it causes contraction of muscles, causing the prostate to squeeze more tightly around the tube, which carries urine. This means that it becomes difficult to pass into urine.</td>
<td>Avoid taking ibuprofen/pseudoephedrine hydrochloride if you experience any problems with prostate or if you have prostate enlargement.</td>
</tr>
<tr>
<td><strong>Liver problems</strong></td>
<td>Both ibuprofen and pseudoephedrine can make liver failure worse.</td>
<td>Patients who already have liver problems must not take ibuprofen/pseudoephedrine hydrochloride, as it could make the liver failure worse.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients who experience yellowing of the eye and/or skin, must stop taking this medicine and consult their doctor, as it may be a sign of liver problems, inflammation of the liver (hepatitis).</td>
</tr>
<tr>
<td><strong>Kidney problems</strong></td>
<td>Both ibuprofen and pseudoephedrine can make kidney failure worse.</td>
<td>Patients who already have kidney problems must not take ibuprofen/pseudoephedrine hydrochloride, as it could make the kidney failure worse.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudoephedrine acts on blood vessels by contracting them. This can cause an increase in the blood pressure and therefore all these conditions can become worse.</td>
</tr>
<tr>
<td><strong>Patients with a particular type of tumour, which causes increased blood pressure, palpitations, increased heart rate and headaches (called phaeochromocytoma), or with glaucoma,</strong></td>
<td>Pseudoephedrine acts on blood vessels by contracting them. This can cause an increase in the blood pressure and therefore all these conditions can become worse.</td>
<td>Avoid taking ibuprofen/pseudoephedrine hydrochloride, if you experience any of these problems.</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td>Advice</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Overactive thyroid and diabetes</strong></td>
<td>Pseudoephedrine acts on blood vessels by contracting them. This can cause an increase in the blood pressure and therefore it blocks all these medicines to function properly.</td>
<td>Ibuprofen/pseudoephedrine hydrochloride must not be taken if patients are on any other medications for treating high blood pressure and heart problems. Please inform your doctor or pharmacist on any other medicines that are being taken, including those obtained without a prescription. This includes herbal medicines.</td>
</tr>
<tr>
<td><strong>Allergic reactions</strong></td>
<td>Allergic reactions can happen due to both ibuprofen and pseudoephedrine. The other ingredients in the product can also cause allergic reactions. Patients who are allergic to other drugs similar to pseudoephedrine or ibuprofen (other NSAIDs) may also be allergic to ibuprofen/pseudoephedrine hydrochloride. Pseudoephedrine hydrochloride may make conditions like asthma worse. Allergic reactions could be severe.</td>
<td>If patients have a history of experiencing any allergic reactions due to ibuprofen, pseudoephedrine or any of the constituents in the product, or if patients have previously shown any allergic reactions (e.g. asthma, swelling of face, lips, mouth and tongue or skin reactions) in response to aspirin or other non-steroidal anti-inflammatory drugs, then ibuprofen/pseudoephedrine hydrochloride must not be taken.</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>There is a possibility that pseudoephedrine may cause the foetus to develop abnormally and therefore the use of ibuprofen/pseudoephedrine hydrochloride during pregnancy should be avoided. During the 3rd trimester, ibuprofen should not be used as it can affect the blood flow from the lungs and the heart of the baby. The onset of labour may be delayed and lengthened, and there is an increase in the risk of bleeding in both mother and child.</td>
<td>Avoid taking ibuprofen/pseudoephedrine hydrochloride during pregnancy.</td>
</tr>
</tbody>
</table>
| **Heart problems**                            | Both ibuprofen and pseudoephedrine can cause an increase in the blood pressure and worsen heart conditions. | Ibuprofen/pseudoephedrine hydrochloride must not be used in patients with severe...
<table>
<thead>
<tr>
<th><strong>Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral suspension</strong></th>
<th><strong>UK/H/5545/001/DC</strong></th>
</tr>
</thead>
</table>

| **Ibuprofen** can cause fluid retention and swelling of ankles in patients with heart failure. | heart, kidney or liver problems.  
There is data to suggest that at high dose of Ibuprofen (above 2400 mg daily) and in long-term treatment, there may be a small increased risk of myocardial infarction (heart attack) or stroke. This is not seen at low doses (e.g. below 1200 mg daily).  
Any risk is more likely with high doses and prolonged treatment. |  
In patients with mild or moderate heart and kidney problems, careful monitoring must be performed, in order to ensure that these conditions are not getting worse.  
Use of the lowest effective dose for the shortest duration must be considered.  
Patients who have heart problems, previous stroke or think that they might be at risk of these conditions (for example if they have high blood pressure, diabetes or high cholesterol or are a smoker), must discuss their treatment with their doctor or pharmacist. |

**Blood reactions**  
Ibuprofen is known to cause blood reactions very rarely. These include anaemia, decrease in white blood cells or abnormal formation of white blood cells.  
There is evidence of an increased risk of blood disorders in HIV patients receiving concurrent treatment with zidovudine (used to treat HIV infection) and ibuprofen.  
Patients must not take this medicine and consult their doctor or pharmacist, if they themselves or their child, are taking zidovudine. |

**Stomach ulcers and bleeding**  
Ibuprofen and other similar drugs (NSAIDs), such as aspirin, can cause stomach ulcers and bleeding. This usually happens if these are taken for long term or more than one NSAID is taken together.  
The risk of bleeding, ulceration or perforation, which can cause death, is higher with increasing NSAID doses, in patients with a history of ulcer (particularly if complicated with bleeding or perforation) and in patients older than 60 years of age.  
If patient has or has ever had stomach ulcers or stomach bleeding, then ibuprofen/pseudoephedrine hydrochloride must not be taken.  
In older people and patients with have previously experienced ulcers, use of the lowest effective dose for the shortest duration must be considered.
**Particular caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding such as oral corticosteroids, anticoagulants such as warfarin, SSRIs or antiplatelet agents such as acetylsalicylic acid.**

Elderly patients are at a higher risk of stomach ulcers and bleeding.

**Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) must be considered for the above mentioned patients and also for patients taking concomitant low-dose acetylsalicylic acid or other medicinal drug products likely to increase gastrointestinal risk.**

Attention must be paid in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease), as these conditions can be worsened.

**Taking other medicines**

- Aspirin and other NSAIDs - there is an increased risk of stomach ulcers and bleeding.
- Medicines used to thin the blood such as warfarin - there is an increased risk of stomach ulcers and bleeding.
- Water tablets (diuretics) and medicines for treating high blood pressure – Ibuprofen may stop these from working well and also may cause kidney problems.
- Corticosteroids - there is an increased risk of stomach ulcers and bleeding.
- Medicines for depression such as lithium – Ibuprofen may increase blood levels of lithium.
- Methotrexate (for arthritis, psoriasis or some cancers) – Ibuprofen may increase blood levels of methotrexate, causing an increase in its toxic effect.
- Antibiotics called quinolones (such as ciprofloxacin) as animal studies have shown that taking ibuprofen with these can increase the risk of convulsions.

**Before taking ibuprofen/pseudoephedrine hydrochloride, please inform your doctor or pharmacist on any other medicines that are being taken, including those obtained without a prescription. This includes herbal medicines.**
## Important potential risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known (Including reason why it is considered a potential risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning a pregnancy</td>
<td>Ibuprofen belongs to a group of medicines which may impair fertility in women. This effect is reversible upon stopping the medicine. It is unlikely that ibuprofen, used occasionally, will affect the chances of becoming pregnant, however, tell your doctor before taking this medicine if you have problems becoming pregnant.</td>
</tr>
<tr>
<td>Aseptic meningitis in patients with certain auto-immune disorders</td>
<td>Single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation, have been observed in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen.</td>
</tr>
<tr>
<td>Severe skin reactions</td>
<td>Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of ibuprofen and other NSAIDs. Patients appear to be at highest risk of these reactions early in the treatment. Stop taking ibuprofen/pseudoephedrine hydrochloride immediately if you see a skin rash, blistering or peeling of the skin.</td>
</tr>
<tr>
<td>Overdose</td>
<td>In children, ingestion of more than 400mg/kg ibuprofen may cause symptoms. Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, drowsiness, occasionally excitation and disorientation or coma are observed. Occasionally patients develop convulsions. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics. Other symptoms of overdosage which may be associated with pseudoephedrine include anxiety, restlessness, irritability, fever, sinus tachycardia, sweating, insomnia, dilated pupils, blurred vision, delusions and hallucinations, muscular weakness, difficulty in micturition, tremors, convulsions, coma, respiratory depression, hypertension, supraventricular and ventricular arrhythmias. If you, your child or someone you know accidentally takes a lot more than the stated dose (an overdose) of this medicine, either call your doctor straight away, or go to your nearest hospital casualty department. Always take any remaining medicine, the container and the label with you, so that the medicine can be identified.</td>
</tr>
<tr>
<td>Cardiovascular thrombotic events</td>
<td>Clinical trials and epidemiological data suggest that the use of ibuprofen, particularly at high doses (above 2400 mg daily) and in long-term treatment, may be associated with a small increased risk of arterial thrombotic events such as heart attack or stroke. Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. below 1200 mg daily) is associated with an increased risk of myocardial infarction.</td>
</tr>
</tbody>
</table>
**IV.7 Discussion on the clinical aspects**

The grant of a marketing authorisation is recommended for this application.

**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 PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*
VI  Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Ibuprofen and pseudoephedrine hydrochloride are well-established active substances. Extensive clinical experience with ibuprofen and pseudoephedrine hydrochloride, in addition to the pharmacokinetic data submitted by the applicant for the use of these actives in combination, is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), package leaflet and labelling text are satisfactory and in line with current guidelines. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and package leaflet for this product are available on the MHRA website.

The currently approved labelling text is listed below:
### LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING (Box) AND IMMEDIATE PACKAGING (Bottle)**

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5ml Oral Suspension

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
   5 ml of suspension contains 100mg of ibuprofen and 15mg of pseudoephedrine hydrochloride.

3. **LIST OF EXCIPIENTS**
   
   It also contains, maltitol, sodium methyl parahydroxybenzonate (E219) and sodium propyl parahydroxybenzoate (E217).

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   Oral suspension
   
   Each bottle contains 100ml of oral suspension. A double-ended 5ml and 2.5ml polypropylene spoon is also included to help measure the dose.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   Read the package leaflet before use.
   
   Oral use

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND THE REACH OF CHILDREN**
   
   Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   EXP: {MM-YYYY}

9. **SPECIAL STORAGE CONDITIONS**

   Do not store above 25°C.
   
   Store in the original container in order to protect from light.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
Boehringer Ingelheim International GmbH
Binger Straße 173,
55216 Ingelheim am Rhein,
Germany

12. MARKETING AUTHORISATION NUMBER(S)
PL 14598/0103

13. BATCH NUMBER
Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY
Supply through pharmacies only

15. INSTRUCTIONS ON USE
Ibuprofen/Pseudoephedrine hydrochloride is effective in clearing a blocked nose and sinuses, relieving aches, pains, headache and feverishness, and easing discomfort of a sore throat.

Adults and adolescents aged 15 years and above:
Depending on the severity of the symptoms 10ml to 20ml every six hours (maximum daily dose 60mls).

Before measuring the dose shake the bottle well until the sediment in the bottle is completely dispersed.

16. INFORMATION IN BRAILLE
Ibuprofen/Pseudoephedrine hydrochloride Oral Suspension
Annex – 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 amend section 4.2 of the SmPC, widening the lower age limit from 16 to 15 years. Consequential changes to sections 4.3 and 4.4, and to the package leaflet.</td>
<td>UK/H/5545/001/II/004</td>
<td>Yes</td>
<td>16/08/2016</td>
<td>09/11/2016</td>
<td>Approval</td>
<td>Y</td>
</tr>
</tbody>
</table>


Annex 1

Our Reference: PL 14598/0103 - 0006
Product: PL 14598/0103 Ibuprofen/Pseudoephedrine hydrochloride 100mg/15mg per 5 ml Oral suspension
Marketing Authorisation Holder: BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Active Ingredient(s): IBUPROFEN, PSEUDOEPHEDRINE HYDROCHLORIDE.

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/5545/001/II/004

Reason:
To amend section 4.2 of the SmPC, widening the lower age limit from 16 to 15 years. Consequential changes to sections 4.3 and 4.4, and to the package leaflet.

Supporting Evidence
The applicant provided a detailed justification for a change in the target population from adults and adolescents aged 16 years and above to adults and adolescents aged 15 years and above in its Clinical Expert Statement, dated 26 July 2016. The applicant provided the following additional clinical data to that presented previously:

- There is no identified pharmacokinetic interaction between ibuprofen and pseudoephedrine hydrochloride; and,
- Two recent UK applications were registered for those 12 years and above (Nurofen Sinus Pressure & Headache Relief Tablets, PL 00063/0718, registered, 30 October 2015 and RobiCold Sinus Relief 200 mg, 30 mg Tab, PL 00165/0391, registered August 2014).

Evaluation
The European guideline cited by the applicant does not specifically discuss management in an adolescent population.

The two cited UK products were based on full dossier applications i.e. 10b (i.e. fixed-dose combination) and 10c (informed consent), which support the indication for 12 years and above.

Of note, Lasynac 200mg/30 mg (ibuprofen 200mg/pseudoephedrine hydrochloride 30mg) film coated tablets, also marketed by Boehringer Ingelheim International GmbH, was granted approval for 15 years and above (UK/H/4352/001/DC; PL 14598/0091) on 22 August 2012.
via a 10(1) application using Rhinadvil 200mg/30mg as the EU reference product. The indications and posology of Lasynac are consistent with the ibuprofen/pseudoephedrine hydrochloride oral suspension under discussion.

**Conclusion**
While the central issue around the most appropriate age for treatment with the ibuprofen/pseudoephedrine hydrochloride combination has been discussed in a previous DCP (with UK as RMS and Germany as CMS), additional information is available that supports the applicant’s claim that there is no quantifiable difference in risk (or change in efficacy) between adolescents aged 15 years and above with those aged 16 years and above.

The fixed dose combination of ibuprofen and pseudoephedrine hydrochloride is approved in adolescents aged 15 years and above in the UK for another marketed product. Furthermore, this age cut-off is also widely accepted across the European Union. In the interest of European harmonisation, and to reduce confusion among health practitioners and the public, the UK recommends the therapeutic indication for Ibuprofen/Pseudoephedrine hydrochloride 100 mg/15 mg per 5 ml Oral Suspension should be changed from ‘Adults and adolescents aged 16 years and above’ to ‘Adults and adolescents aged 15 years and above’. The proposed changes to sections 4.2 and 4.3 of the SmPC and the Package Leaflet are acceptable.

The updated SmPC and PIL are available on the Medicines and Healthcare products Regulatory Agency website. The approved labelling text can be found above.

**Decision:** Approved

**Date:** 09 November 2016