Public Assessment Report

Decentralised Procedure

RobiCold Cold & Flu Relief 200 mg / 30 mg Soft Capsules

Ibuprofen/ Pseudoephedrine hydrochloride Pfizer 200 mg/ 30 mg Capsules

(Ibuprofen and pseudoephedrine hydrochloride)

Procedure numbers: UK/H/5670-5671/001/E/001

UK Licence Numbers: PL 00165/0388-0389

Pfizer Consumer Healthcare Ltd.
LAY SUMMARY
RobiCold Cold & Flu Relief 200 mg / 30 mg Soft Capsules
Ibuprofen/Pseudoephedrine hydrochloride Pfizer 200 mg / 30 mg Capsules
(Ibuprofen and pseudoephedrine hydrochloride, soft capsules, 200 mg/30 mg)

This is a summary of the Public Assessment Report (PAR) for RobiCold Sinus Relief 200 mg / 30 mg Soft Capsules (PL 00165/0388; UK/H/5670/001/DC) and Ibuprofen/Pseudoephedrine hydrochloride Pfizer 200 mg/ 30 mg Capsules (PL 00165/0389; UK/H/5671/001/DC). It explains how RobiCold Sinus Relief 200 mg / 30 mg Soft Capsules and Ibuprofen/Pseudoephedrine hydrochloride Pfizer 200 mg/ 30 mg Capsules 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 RobiCold Sinus Relief 200 mg / 30 mg Soft Capsules and Ibuprofen/Pseudoephedrine hydrochloride Pfizer 200 mg / 30 mg Capsules.

The products will be collectively referred to as Ibuprofen/Pseudoephedrine hydrochloride Capsules throughout the remainder of this public assessment report (PAR).

For practical information about using Ibuprofen/Pseudoephedrine hydrochloride Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Ibuprofen/Pseudoephedrine hydrochloride Capsules and what are they used for?
RobiCold Cold & Flu Relief 200 mg / 30 mg Soft Capsules (PL 00165/0388; UK/H/5670/001/DC) are used to treat symptoms of the common cold and flu, including headache, high temperature (fever), sore throat, aches and pains, blocked nose in adults and young people aged 12 and over.

Ibuprofen/ Pseudoephedrine hydrochloride Pfizer 200 mg/ 30 mg Capsules (PL 00165/0389; UK/H/5671/001/DC) are used to treat symptoms of the common cold and flu, including headache, high temperature (fever), sore throat, aches and pains, blocked nose in adults and young people aged 15 and over.

The patient must only use this medicine if they have a blocked nose together with headache and high temperature. The patient must not use this medicine if they only have one of the symptoms listed above.

How do Ibuprofen/Pseudoephedrine hydrochloride Capsules work?
This medicine contains two active substances, ibuprofen and pseudoephedrine hydrochloride.
• Ibuprofen belongs to a group of medicines called ‘non-steroidal anti-inflammatory drugs’ (NSAIDs). It helps to reduce pain and lower a high temperature (fever).
• Pseudoephedrine hydrochloride belongs to a group of medicines called ‘vasoconstrictors’. It helps to clear the nasal passages and eases nasal congestion.

How are Ibuprofen/Pseudoephedrine hydrochloride Capsules used?
The pharmaceutical form of Ibuprofen/Pseudoephedrine hydrochloride Capsules is a capsule (soft) and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as described in the package leaflet or as their doctor or pharmacist has told them. The patient must check with their doctor or pharmacist if they are not sure.
The recommended dose is 1 capsule every 4 to 6 hours. If the patient’s symptoms are more severe they can take 2 capsules at the same time. The patient must not take more than 6 capsules in 24 hours.

The patient should swallow the capsules whole with a large glass of water.
The patient should not take this medicine for more than 5 days.

This medicine is for short term use only; the patient should take the lowest dose for the shortest time necessary to treat their symptoms.

The patient must talk to their doctor if they do not feel better or if they feel worse after 5 days. The patient’s doctor will tell them if it is safe to carry on taking this medicine.

Please refer to section 3 of the package leaflet for information on how to use this medicine.

This medicine can be obtained without a prescription.

For further information on how Ibuprofen/Pseudoephedrine hydrochloride Capsules are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**What benefits of Ibuprofen/Pseudoephedrine hydrochloride Capsules have been shown in studies?**

The company provided its own data on efficacy and safety studies. These studies have shown that Ibuprofen/Pseudoephedrine hydrochloride Capsules is effective in treating symptoms of the common cold and flu, including headache, high temperature (fever), sore throat, aches and pains, blocked nose in adults and young people aged 12 (RobiCold Cold & Flu Relief 200 mg / 30 mg Soft Capsules) or aged 15 (Ibuprofen/ Pseudoephedrine hydrochloride Pfizer 200 mg/ 30 mg Capsules) and over.

**What are the possible side effects of Ibuprofen/Pseudoephedrine hydrochloride Capsules?**

The most common side effects with Ibuprofen/Pseudoephedrine hydrochloride Capsules (which may affect up to 1 in 10 people) are:

- feeling sick (nausea)
- bleeding from the stomach or bowel, signs include vomiting blood, blood in faeces, or black coloured faeces.

For the full list of all side effects reported with Ibuprofen/Pseudoephedrine hydrochloride Capsules, see section 4 of the package leaflets available on the MHRA website.

**Why were Ibuprofen/Pseudoephedrine hydrochloride Capsules approved?**

The MHRA decided that this medicine’s benefits are greater than its risks and recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of Ibuprofen/Pseudoephedrine hydrochloride Capsules?**

A risk management plan (RMP) has been developed to ensure that Ibuprofen/Pseudoephedrine hydrochloride Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflets for Ibuprofen/Pseudoephedrine hydrochloride Capsules including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Ibuprofen/Pseudoephedrine hydrochloride Capsules
For RobiCold Cold & Flu Relief 200 mg / 30 mg Soft Capsules (PL 00165/0388; UK/H/5670/001/DC), Ireland, Malta, Romania, the Slovak Republic and the UK agreed to grant Marketing Authorisations on 23 December 2015. A Marketing Authorisation was granted in the UK on 20 January 2016. A repeat-use procedure to add the Czech Republic and Hungary as concerned member states was completed on 17 February 2017 (UK/H/5670/001/E/001). The product name was changed to RobiCold RobiCold Cold & Flu Relief 200 mg / 30 mg Soft Capsules by a variation granted on 09 August 2016.

For Ibuprofen/ Pseudoephedrine hydrochloride Pfizer 200 mg/ 30 mg Capsules (PL 00165/0389; UK/H/5671/001/DC), Germany, Poland and the UK agreed to grant Marketing Authorisations on 23 December 2015. A Marketing Authorisations was granted in the UK on 20 January 2016. A repeat-use procedure to add Germany, France and Poland as concerned member states was completed on 17 February 2017 (UK/H/5671/001/E/001).

The full PAR for Ibuprofen/Pseudoephedrine hydrochloride Capsules, follows this summary.

For more information about treatment with Ibuprofen/Pseudoephedrine hydrochloride Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2017.
TABLE OF CONTENTS

I Introduction ........................................... Page 6
II Quality aspects ........................................ Page 8
III Non-clinical aspects ................................. Page 11
IV Clinical aspects ....................................... Page 11
V User consultation ...................................... Page 21
VI Overall conclusion, benefit/risk assessment and recommendation .................................. Page 22

Table of content of the PAR update for MRP and DCP .................................................. Page 26

Annex 1 .................................................... Page 27
I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Ibuprofen/Pseudoephedrine hydrochloride Capsules, (PL 00165/0388-0389; UK/H/5670-5671/001/DC), is approved. These fixed-dose combination products are available without a prescription and are supplied through pharmacies only (legal classification P) and are indicated:

RobiCold Sinus Relief 200 mg / 30 mg Soft Capsules:
- for the relief of symptoms of the common cold and flu such as headache, fever, sore throat, minor aches and pain when associated with blocked nose (nasal congestion) and sinuses (sinusitis) in adults and adolescents over 12 years of age.

Ibuprofen/ Pseudoephedrine hydrochloride Pfizer 200 mg/ 30 mg Capsules:
- for the relief of symptoms of the common cold and flu such as headache, fever, sore throat, minor aches and pain when associated with blocked nose (nasal congestion) and sinuses (sinusitis) in adults and adolescents over 15 years of age.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and:

- For RobiCold Sinus Relief 200 mg / 30 mg Soft Capsules (PL 00165/0388; UK/H/5670/001/DC): Ireland, Malta, Romania and the Slovak Republic as Concerned Member States (CMS).
- For Ibuprofen/ Pseudoephedrine hydrochloride Pfizer 200 mg/ 30 mg Capsules (PL 00165/0389; UK/H/5671/001/DC): Germany and Poland as Concerned Member States (CMS).

The applications were submitted under Article 8(3) of Directive 2001/83/EC, as amended, for a new product with known active substances (mixed dossier).

Ibuprofen/pseudoephedrine hydrochloride fixed dose combinations have been available in the EU for over 20 years and are a widely used over the counter to treat the symptoms of a cold/flu. Pfizer Consumer Healthcare Ltd hold licences in a number of EU countries for the proposed combination in tablet form, but not the soft gelatin capsule proposed.

Ibuprofen is a non-selective inhibitor of cyclo-oxygenase (COX)-1 and COX-2. It is a chiral compound and its pharmacological activity is mainly dependent on the S(+) enantiomer. The principal pharmacodynamic actions of ibuprofen, like that of other NSAIDs, that are involved in control of acute pain, fever and acute inflammatory reactions are the inhibition of COX-1 and COX-2 derived proinflammatory prostanoids (mainly prostaglandin E2 [PGE2]). Pain relief is attributed to peripheral (anti-inflammatory) and CNS effects of S(+) ibuprofen on the inducible COX-2 and inducible nitric oxide synthase (iNOS)/constitutive nitric oxide synthase (cNOS) present in inflamed or inflammatory cells of the peripherally affected regions as well as in the dorsal horn and higher spino-thalamic tracts mediating pain transmission. There may be some contribution of inhibition of COX-1 in the central nervous system (CNS) to the analgesic actions of ibuprofen.

Pseudoephedrine hydrochloride is a sympathomimetic vasoconstrictor. It has mainly indirect agonist activity, particularly on cardiac β receptors, leading to increased cardiac output and to relaxation of bronchial smooth muscles. Its actions on peripheral α1 receptors, through displacement of noradrenaline from the cytoplasmic pool, lead to an increase in systolic blood pressure (SBP). Its action on α adrenoceptors in the mucosa of the respiratory tract produces a degree of vasoconstriction which leads to a reduction in mucosal oedema. It also has a weak central nervous system stimulant action, especially in patients sensitive to sympathomimetic drugs.

No new non-clinical studies were conducted, which is acceptable given that the applications are for new products containing well-known active substances.
Bibliographic data on ibuprofen and pseudoephedrine hydrochloride have been submitted to support these applications. The applicant has also supplied a bioavailability study using their formulation, a licenced UK ibuprofen/pseudoephedrine hydrochloride tablet and an ibuprofen soft capsule so that they may bridge to the available bibliographic data. In addition to the bibliographic data and bioavailability study, the applicant has provided an interaction study and 4 clinical efficacy studies to support these applications. The applicant has stated that the bioavailability study was conducted according to Good Clinical Practice (GCP) principles. The other studies submitted by the applicant were performed during the 1980’s prior to the development and implementation of Good Clinical Practice (GCP)/International Conference on Harmonization (ICH). In these studies, objective and subjective assessments were used to assess the efficacy and safety of ibuprofen/pseudoephedrine hydrochloride in the proposed indication.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (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.

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.

For RobiCold Sinus Relief 200 mg / 30 mg Soft Capsules (PL 00165/0388; UK/H/5670/001/DC), Ireland, Malta, Romania, the Slovak Republic and the UK agreed to grant Marketing Authorisations on 23 December 2015. A Marketing Authorisation was granted in the UK on 20 January 2016. A repeat-use procedure to add the Czech Republic and Hungary as concerned member states was completed on 17 February 2017 (UK/H/5670/001/E/001). The product name was changed to RobiCold Cold & Flu Relief 200 mg / 30 mg Soft Capsules by a variation granted on 09 August 2016.

For Ibuprofen/ Pseudoephedrine hydrochloride Pfizer 200 mg/ 30 mg Capsules (PL 00165/0389; UK/H/5671/001/DC), Germany, Poland and the UK agreed to grant Marketing Authorisations on 23 December 2015. A Marketing Authorisation was granted in the UK on 20 January 2016. A repeat-use procedure to add Germany, France and Poland as concerned member states was completed on 17 February 2017 (UK/H/5671/001/E/001).
II QUALITY ASPECTS

II.1 Introduction
Each soft capsule contains 200 mg ibuprofen and 30 mg pseudoephedrine hydrochloride, as the active ingredients. Other ingredients consist of the pharmaceutical excipients:

Soft Fill:
Potassium hydroxide, macrogel 600 and purified water.

Gelatin Capsule:
Sorbitol soft, partially dehydrated (E 420), gelatin, black printing ink [consisting of macrogel 400, polyvinyl acetate phthalate, propylene glycol and iron oxide black (E172)] and soya lecithin in triglycerides, medium chain.

The finished product is packaged in the following presentations:
- white, opaque, PVC/PVdC heat sealed to glassine/aluminium foil blister strips
- white, opaque, PVC/PE/PVdC heat sealed to glassine/aluminium foil blister strips

The blister strips are packed into outer cardboard cartons in pack sizes of 2, 4, 8, 10, 12, 16, 20, and 24 capsules.

Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substances
(1) Ibuprofen
INN: Ibuprofen
Chemical name: (2RS)-2-[4-(2-Methylpropyl)phenyl] propanoic acid.
Structure:

Molecular formula: C₁₃H₁₈O₂
Molecular weight: 206.3 g/mol
Description: 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 a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

(2) Pseudoephedrine hydrochloride
INN: Pseudoephedrine hydrochloride
Chemical name: (1S,2S)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride
Structure:
Molecular formula: $C_{10}H_{16}ClNO$
Molecular weight: 201.7 g/mol
Description: 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.

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 objective of the development programme was to formulate safe, efficacious, soft capsules containing 200 mg ibuprofen and 30 mg pseudoephedrine hydrochloride, as the active ingredients. A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of potassium hydroxide and the black printing ink which are controlled to suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from EDQM to show that they are manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these products.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform additional process validation on future commercial scale batch sizes.
Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions “Store below 30°C.”

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

A variation to change the shelf-life to 3 years and to change the storage conditions to “store below 25°C” was granted on 07 September 2017.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.
III. NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen and pseudoephedrine hydrochloride 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 Ecotoxicity/environmental risk assessment (ERA)
The Applicant conducted a comprehensive review of the available literature for ibuprofen and pseudoephedrine hydrochloride and provided an environmental risk assessment based on relevant published studies and other available information.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of these applications from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV.1 Introduction
One bioavailability study was submitted to support this application using the applicant’s formulation of a licenced UK ibuprofen/pseudoephedrine hydrochloride tablet and an ibuprofen soft capsule so that the applicant may bridge to the available bibliographic data.

The applicant has also provided an interaction study to demonstrate there is no interaction between ibuprofen and pseudoephedrine hydrochloride in combination and 4 clinical efficacy studies, conducted in the 1980s comparing a hard capsule formulation at different doses to placebo.

With the exception of the bioavailability study, interaction study and 4 clinical efficacy studies no new 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 and phenylephrine hydrochloride.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In support of these applications, the applicant submitted the following interaction and bioavailability study:

STUDY 1
Absence of Interaction between ibuprofen and pseudoephedrine hydrochloride study
This was a randomised, 3-way crossover study, which verified there was no pharmacokinetic interaction between the 2 components. Healthy volunteers received a single dose of each of the following:

- Advil® 200 mg (ibuprofen) 2 tablets
- Sudafed® 30 mg (pseudoephedrine) 2 tablets
- Advil® 200 mg and Sudafed® 30 mg 2 tablets of each

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. Urine samples were collected 0-24 and 24-48 hours after the dose. Ibuprofen and pseudoephedrine hydrochloride plasma levels were assayed by high-performance soft chromatography (HPLC).

The pharmacokinetic results are presented below:

### Table: Summary of pharmacokinetic parameters for test and reference product for the actives ibuprofen and pseudoephedrine hydrochloride (least squares geometric means, 90% confidence interval (CI) of ratio):

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>Treatment A (2 x 200 mg Advil)</th>
<th>Treatment B (2 x 30 mg Sudafed)</th>
<th>Treatment C (2 x 200 mg Advil / 2 x 30 mg Sudafed)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ibuprofen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>µg/mL</td>
<td>42.1 ± 10.9</td>
<td>-</td>
<td>38.6 ± 9.24</td>
<td>NS</td>
</tr>
<tr>
<td>C_{max}</td>
<td>µg/mL</td>
<td>146 ± 53.3</td>
<td>-</td>
<td>140 ± 34.8</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Pseudoephedrine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max}</td>
<td>ng/mL</td>
<td>-</td>
<td>211 ± 44.9</td>
<td>213 ± 35.8</td>
<td>NS</td>
</tr>
<tr>
<td>AUCI</td>
<td>ng/mL</td>
<td>1573 ± 668</td>
<td>1889 ± 564</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

C_{max} = maximum observed drug concentration; AUCI = area under the drug concentration-time curve from time 0 to infinity; NS = not significant.

No significant difference was observed in AUCI or C_{max} when ibuprofen and pseudoephedrine hydrochloride were administered simultaneously compared to each ingredient administered separately. Ibuprofen/pseudoephedrine hydrochloride exhibited an equivalent rate (C_{max}) and extent (AUCI) of absorption compared to each ingredient administered separately, as the 90% confidence interval for each respective ratio was within the accepted range of 80% to 125% (after re-analysis of the parameters AUCI and C_{max} to assess the rate and extent of absorption by current methods as detailed below).

The study was conducted in 1987 and statistically analysed prior to the establishment of current statistical rules for evaluating bioequivalence. A re-analysis of the maximum observed drug concentration (C_{max}) and the area under the drug concentration-time curve from time 0 to infinity (AUCI) was performed to assess the rate and the extent of absorption by current methods. The data for each of the above parameters, transformed logarithmically, were analysed via an analysis of variance (ANOVA) model with subject, treatment and treatment period terms in the model. Based on the fitted model, 90% 2-sided confidence intervals were constructed for each test/reference ratio. For a given comparison and a given parameter, bioequivalence was considered achieved if the 90% confidence interval for the test/reference ratio was contained within the accepted range of 80% to 125%.
Table: Summary of results: Re-analysis of pharmacokinetic parameters for the active ibuprofen.

<table>
<thead>
<tr>
<th>Summary Statistics</th>
<th>C_max (mcg/mL) Mean (SD)</th>
<th>AUCI (hr.mcg/mL) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: 2x IBU tablets</td>
<td>42.11 (10.9)</td>
<td>146.3 (53.3)</td>
</tr>
<tr>
<td>(n=17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C: 2 x IBU + PSE capsules</td>
<td>38.56 (9.2)</td>
<td>140.1 (34.8)</td>
</tr>
<tr>
<td>(n=17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test/reference ratio and 90% CI (%)</td>
<td>108.3 (98.8, 118.7)</td>
<td>101.2 (91.9, 111.6)</td>
</tr>
<tr>
<td>A vs. C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(C_{\text{max}}\) = maximum observed drug concentration; \(\text{AUCI}\) = area under the drug concentration-time curve from time 0 to infinity; \(\text{IBU} = \text{ibuprofen}; \text{PSE} = \text{pseudoephedrine}; \text{SD} = \text{standard deviation}; \text{CI} = \text{confidence interval}.\) Note: Ratios and the confidence intervals are based on the statistical model fitted to the log transformed data.

Table: Summary of results: Re-analysis of pharmacokinetic parameters for the active pseudoephedrine hydrochloride.

<table>
<thead>
<tr>
<th>Summary Statistics</th>
<th>C_max (ng/mL) Mean (SD)</th>
<th>AUCI (hr.ng/mL) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B: 2 x PSE tablets</td>
<td>211.1 (44.9)</td>
<td>1972.6 (667.9)</td>
</tr>
<tr>
<td>(n=17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C: 2 x IBU + PSE capsules</td>
<td>213.0 (35.8)</td>
<td>1888.8 (563.8)</td>
</tr>
<tr>
<td>(n=17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test/reference ratio and 90% CI (%)</td>
<td>97.6 (90.7, 105.0)</td>
<td>103.0 (93.6, 113.2)</td>
</tr>
<tr>
<td>B vs. C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(C_{\text{max}}\) = maximum observed drug concentration; \(\text{AUCI}\) = area under the drug concentration-time curve from time 0 to infinity; \(\text{IBU} = \text{ibuprofen}; \text{PSE} = \text{pseudoephedrine}; \text{SD} = \text{standard deviation}; \text{CI} = \text{confidence interval}.\) Note: Ratios and the confidence intervals are based on the statistical model fitted to the log transformed data.

Interaction study conclusion
The applicant has adequately summarised the absorption of the actives and shown in the presented study that there are no significant interactions between the actives. The re-analysis further confirms this using the current bioequivalence methodology.

STUDY 2
Bioavailability comparison study between the applicant’s proposed formulation, a licenced ibuprofen/pseudoephedrine hydrochloride tablet and an ibuprofen soft capsule.

The bioavailability study described below was conducted to support registration in the EU and demonstrate:

- bioequivalence between the proposed European soft capsule and the European reference product, Nurofen Cold & Flu (PL 00063/0375; a tablet formulation containing 200 mg ibuprofen and 30 mg pseudoephedrine hydrochloride), which was granted a licence in the United Kingdom (UK) in 1993;
- bioequivalence of ibuprofen between the proposed European soft capsule and the ibuprofen single entity soft capsule (Anadin LiquiFast 200 mg Capsules; PL 00165/0142) that has been marketed in the EU since 2005;

...to bridge the safety and efficacy data of the currently marketed European products.

The study was a single-dose, randomised, open-label, in-patient, 3-way crossover, single-centre, bioavailability study. Healthy subjects were randomly assigned to 1 to 6 dosing sequences and received 1 of the 3 treatments in each study period (ibuprofen plus pseudoephedrine hydrochloride soft capsule formulation, ibuprofen plus pseudoephedrine hydrochloride tablet formulation, or ibuprofen soft capsule formulation). Each treatment period was separated by at least 48 hours. Subjects were administered the
test or reference product, following an overnight fast of at least 10 hours. Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration.

The study was to be deemed successful if:

a. the pseudoephedrine hydrochloride in the ibuprofen plus pseudoephedrine hydrochloride soft capsule is bioequivalent to the pseudoephedrine hydrochloride in the ibuprofen plus pseudoephedrine hydrochloride tablet based on log transformed values of the area under the drug concentration-time curve from time 0 to time t, the time of the last measurable concentration (AUCL) and C_max and

b. the ibuprofen in the ibuprofen plus pseudoephedrine hydrochloride soft capsule is bioequivalent to the ibuprofen in the ibuprofen soft capsule or if the bioavailability falls between the two reference products based on log transformed values of AUCL and C_max.

Table: Bioequivalence results for ibuprofen

<table>
<thead>
<tr>
<th></th>
<th>C_max (mcg/mL)</th>
<th>AUCL (mcg*hr/mL)</th>
<th>AUCI (mcg*hr/mL)</th>
<th>T_max (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD), Median</td>
<td>25.1 (6.22)</td>
<td>72.6 (15.60)</td>
<td>74.0 (16.11)</td>
<td>56.5 (43.20), 39.0</td>
</tr>
<tr>
<td>IBU + PSE soft capsule (A)</td>
<td>19.7 (5.80)</td>
<td>70.9 (14.62)</td>
<td>72.7 (15.40)</td>
<td>100.6 (91.87), 67.5</td>
</tr>
<tr>
<td>IBU soft capsule (C)</td>
<td>23.6 (7.26)</td>
<td>70.0 (14.66)</td>
<td>71.7 (15.03)</td>
<td>60.7 (50.24), 45.0</td>
</tr>
<tr>
<td>Ratio (%) (90% CI)</td>
<td>129.50</td>
<td>102.11</td>
<td>101.81</td>
<td></td>
</tr>
<tr>
<td>A/B</td>
<td>(118.40, 141.65)</td>
<td>(99.82, 104.46)</td>
<td>(99.55, 104.11)</td>
<td></td>
</tr>
<tr>
<td>A/C</td>
<td>108.71</td>
<td>103.74</td>
<td>103.29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(99.39, 118.92)</td>
<td>(101.41, 106.13)</td>
<td>(101.02, 105.61)</td>
<td></td>
</tr>
</tbody>
</table>

For the AUC parameters, the 90% confidence interval (CI) was within the acceptance range (80%, 125%) for bioequivalence. As expected, the 90% CI for the C_max was not within the acceptance range for bioequivalence. Each of the 90% CIs for the geometric mean ratios (%) of ibuprofen plus pseudoephedrine hydrochloride soft capsule to ibuprofen soft capsule were contained entirely within the acceptance range (80%, 125%) for bioequivalence. Median (mean) time to peak exposure (T_max) was comparable between ibuprofen plus pseudoephedrine hydrochloride soft capsule and ibuprofen soft capsule, and was 20-30 (40-50) minutes shorter than for ibuprofen plus pseudoephedrine hydrochloride tablet. These results are consistent with the pre-specified criteria listed in the study report.
The 90% CIs for the geometric mean ratios (%) of ibuprofen plus pseudoephedrine hydrochloride soft capsule to ibuprofen plus pseudoephedrine hydrochloride tablet ratios were contained entirely within the (80%, 125%) acceptance range for bioequivalence. Median (mean) time to peak exposure (T\text{max}) for the ibuprofen plus pseudoephedrine hydrochloride soft capsule formulation was about 30 (10) minutes longer than the tablet formulation.

**Bioavailability study conclusion**

The bioavailability study was adequately designed to address the bridging over to the bibliographic data for the rest of the application. It is agreed that the study has met its objectives in that pseudoephedrine hydrochloride has been shown to be bioequivalent between the test and reference. As expected ibuprofen in the soft capsule formulations showed bioequivalence but when compared to the tablet formulation, T\text{max} was earlier and C\text{max} was higher. The AUC is considered equivalent. These results reflect what has been seen in previous studies.

**Overall conclusions on pharmacokinetics**

The applicant has adequately summarised the absorption, distribution, metabolism and excretion of both actives alone and in combination. With the interaction study they have shown that there is no interaction between ibuprofen and pseudoephedrine hydrochloride in the combination. An adequate discussion of renal impairment is supplied.

The applicant has also supplied details of a bioavailability study using their formulation, a licenced UK ibuprofen/pseudoephedrine hydrochloride tablet and an ibuprofen soft capsule so that they may bridge to the available bibliographic data. The study, as expected showed bioequivalence for pseudoephedrine. It also, as expected, showed that whilst overall exposure was comparable (AUC) with the tablet combination, it had an earlier T\text{max} and higher C\text{max}. The applicant’s formulation was bioequivalent with regards to ibuprofen with the single active UK licenced ibuprofen soft capsule formulation. It is therefore accepted that bridging to available bibliographic data is acceptable.

**IV.3 Pharmacodynamics**

The applicant has adequately summarised the pharmacodynamics of the actives. As such they are expected to act on different symptoms associated with a cold/flu. The application also adequately summarised any expected pharmacodynamic interactions.
IV.4 Clinical efficacy
Ibuprofen/pseudoephedrine hydrochloride fixed dose combinations have been available in the EU for over 20 years and are a widely used over the counter to treat the symptoms of a cold/flu symptomatic treatment. As stated above, the applicant has bridged to the available data in the bioavailability study above.

The applicant has provided four studies, conducted in the 1980s comparing a hard capsule formulation at different doses to placebo. However, only two studies are in the correct disease model- upper respiratory tract infection. The applicant has attempted to justify the inclusion of data from two studies in allergic rhinitis but whilst some of the symptoms may be similar the underlying pathology is not and many symptoms are missing from allergic rhinitis that are present in URTI. Therefore, these 2 studies will not be discussed further. The 2 studies submitted of relevance are discussed below:

STUDY 3
This double-blind, placebo-controlled, single-dose, randomised, parallel-group study with 3 treatment groups aimed to demonstrate the safety and efficacy of ibuprofen 200 mg with pseudoephedrine hydrochloride 30 mg when compared with ibuprofen 400 mg with pseudoephedrine hydrochloride 60 mg and matching placebo in an out-patient population with nasal congestion associated with acute URTI.

Patients of generally good health, but with a clinical diagnosis of URTI with onset of less than 5 days and accompanying symptoms of moderate to severe nasal congestion (as indicated by a baseline score greater than 50 mm on the 100 mm Nasal Congestion Scale [NCS]) were eligible to enter the study.

Subjects were randomised under double-blind conditions to receive a single, oral, 2-hard capsule dose of either:
• Ibuprofen 400 mg/pseudoephedrine hydrochloride 60 mg,
• Ibuprofen 200 mg/pseudoephedrine hydrochloride 30 mg; or
• Placebo.
All doses were given in 2 identically-appearing hard capsules.

Efficacy measurements:
Nasal Congestion Scale (NCS): 100-mm visual analog scale (0 mm = not at all, 100 mm = very much).
Nasal Congestion Relief Rating (NCRR): 6-Category Relief Scale (0 = no relief, 5 = complete relief).
Baseline NCS score was obtained pre-treatment. NCS and NCRR measurements were made at 0.5, 1, 1.5, 2, 3 and 4 hours after dosing.

Results
Table: Sum of nasal congestion differences analysis of covariance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IBU400/PSE60 (N=100)</th>
<th>IBU200/PSE30 (N=100)</th>
<th>Placebo (N=100)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>76.9</td>
<td>28.4</td>
<td>5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SD</td>
<td>43.7</td>
<td>13.3</td>
<td>18.0</td>
<td></td>
</tr>
</tbody>
</table>

IBU = ibuprofen; PSE = pseudoephedrine; ANOVA = analysis of covariance; SD = standard deviation.
P-value of ANOVA with baseline, treatment and gender in the model
PAR RobiCold Cold & Flu Relief 200 mg / 30 mg Soft Capsules
Ibuprofen/Pseudoephedrine hydrochloride Pfizer 200 mg / 30 mg Capsules

Table: Sum of relief of nasal congestion analysis of covariance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IBU400/PSE60 (N=100)</th>
<th>IBU200/PSE30 (N=100)</th>
<th>Placebo (N=100)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>6.5</td>
<td>2.7</td>
<td>0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SD</td>
<td>3.0</td>
<td>1.4</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

IBU = ibuprofen; PSE = pseudoephedrine; ANOVA = analysis of covariance; SD = standard deviation.
P-value of ANOVA with baseline, treatment and gender in the model.

In this study, statistically significant differences in the proportion of men and women in the placebo group (males = 43%) compared to the ibuprofen 200 mg/pseudoephedrine hydrochloride 30 mg (males = 23%) and ibuprofen 400 mg/pseudoephedrine hydrochloride 60 mg (males = 26%) groups were found (p=0.004). Evaluation of the baseline ratings with gender as a factor in the model, yielded a gender-by-treatment interaction (p=0.034), but no overall gender effect (p=0.308). The interaction was related to the lower mean baseline scores for males in the ibuprofen 400 mg/pseudoephedrine hydrochloride 60 mg group and the reverse in the ibuprofen 200 mg/pseudoephedrine hydrochloride 30 mg group.

Study conclusion
This simple study demonstrated that in subjective measures of nasal congestion, the combination was more effective than placebo and showed a dose related increase in efficacy. However, it is noted that the study only looked at subjective scores and did not measure patency or airflow and also only concentrated on one aspect of the symptoms usually seen in colds and flu. As such it provides good evidence for nasal congestion but not pain, fever or other symptoms of colds/flu.

STUDY 4
This was a double blind, placebo-controlled, variable-dose, parallel, in-use study. The primary objective of this clinical trial was to assess the safety of the combination of ibuprofen and pseudoephedrine hydrochloride in an “actual-use” setting, as the efficacy of the ibuprofen/pseudoephedrine hydrochloride combination had been evaluated in the previous study. Therefore, a safety-in-use study was designed on subjects who had upper respiratory tract infection (URTI) symptoms for which self-medication would be appropriate. A global evaluation of the efficacy of the ibuprofen/pseudoephedrine hydrochloride combination was collected as a secondary objective.

A safe and effective OTC combination drug (paracetamol/pseudoephedrine hydrochloride) was employed as a positive control and a placebo group was used as a negative control. Subjects were randomly allocated to 1 of the 3 treatment groups in the ratio of 2:2:1:
- Ibuprofen/pseudoephedrine hydrochloride 200 mg/30 mg per hard capsule;
- Paracetamol/pseudoephedrine hydrochloride 500 mg/30 mg per hard capsule;
- Placebo.

Patients were instructed to take 1 hard capsule every 4-6 hours as needed. If symptoms were not relieved by 1 hard capsule, a second hard capsule could be taken, but not more than 6 hard capsules within a 24-hour period. The duration of treatment could extend up to 10 days, depending on each subject’s symptoms and perceived need for medication. At the same time each evening, subjects were asked to record “anything unusual which you think might be caused by the study medication”. The severity of each reported side effect was rated on a 3-point scale (mild, moderate, severe). Patients were further instructed to rate the effectiveness of the study medication by completing a 4-point categorical Global Evaluation Scale (0 = not effective, 3 = very effective). On the day following their final dose of study medication, patients were instructed to return to the study site for a follow-up examination.
Adult subjects presenting with acute URTI of less than 1 week’s duration were eligible to be enrolled in this clinical trial if they had symptom(s) of URTI (eg, nasal congestion, runny nose, post-nasal drip, sinus congestion) and at least 1 symptom requiring an analgesic (eg, sore throat, headache) or an antipyretic.

Criteria for evaluation:
Safety: adverse events recorded daily by the patients.
Efficacy evaluated daily by completing a 4-point categorical global evaluation scale (0 to 3).

Results
An analysis of the subject dosing pattern based on 711 efficacy-analysable patients found that 33% of the subjects took a mean daily dose of 1.0 to 1.25 hard capsules, 63% took more than 1.25 and less than 1.75 hard capsules and 4% took 1.75 to 2.0 hard capsules per day throughout the study. This pattern was noted across the 3 treatment groups. More placebo-treated patients took 2-hard capsule doses between Days 1 and 3 than the patients in the 2 active treatment groups (no formal statistical tests were performed).

Analysis of the Global Evaluation was performed on each study day. Treatment comparisons based on Day 1 data showed that both ibuprofen/pseudoephedrine hydrochloride and paracetamol/pseudoephedrine hydrochloride were superior to placebo (p <0.05). Highly significant (p <0.001) treatment-by-investigator interactions were detected on Days 2 through 9. Consequently, the pooled results after Day 1 were considered unreliable since the nature of such significant interaction was due to the reversal of drug effect at 1 centre. Since 1 centre showed a drug effect in the opposite direction to the results of the remaining centres, the strategy employed was to exclude the 96 patients from that centre and perform a separate pooled analysis based on 615 patients from the remaining centres. Results of this analysis showed that both ibuprofen/pseudoephedrine hydrochloride and paracetamol/pseudoephedrine hydrochloride were superior to placebo from Day 1 through Day 6 (p <0.05). No treatment differences between the 2 active treatments were observed.

Analyses of the responses of the 235 subjects at all sites who took predominantly 1 hard capsule per dose (ie, a mean daily dose of 1.0 to 1.25 hard capsules) throughout the trial (ibuprofen/pseudoephedrine hydrochloride = 97, paracetamol/pseudoephedrine hydrochloride= 94, placebo = 44) demonstrated that ibuprofen/pseudoephedrine hydrochloride was more effective than placebo from Day 1 through Day 4 (p <0.05) and for the average responses throughout the trial (p <0.05). Mean responses for the paracetamol/pseudoephedrine hydrochloride group were significantly greater than those of the placebo group on Day 1 and Day 4 (p <0.05).

There was a clear separation of both active medications from placebo on each day of the study and overall. The efficacy of the lower dose combination containing ibuprofen 200 mg with pseudoephedrine hydrochloride 30 mg was also demonstrated: subjects in the ibuprofen/pseudoephedrine hydrochloride group who took predominantly 1 hard capsule per dose reported greater relief than the placebo subjects (p <0.05).
Mean values of Global evaluation (all 711 efficacy-analysable patients):

![Graph showing mean values of Global evaluation](image)

I/P = ibuprofen/pseudoephedrine; A/P = paracetamol/pseudoephedrine; Pbo = Placebo.
Note: There was a decrease of sample size over time for all 3 treatments.

Mean values of global evaluation (235 “predominantly 1” patients):

![Graph showing mean values of global evaluation](image)

I/P = ibuprofen/pseudoephedrine; A/P = paracetamol/pseudoephedrine; Pbo = Placebo.
Note: There was a decrease of sample size over time for all 3 treatments.

**Study conclusion**
This simple study looking at a “global evaluation” shows that both combinations were more effective in this measure than placebo, however there is no breakdown on specific symptoms and measures that were
used during the study. As such, the study is of limited use in establishing the efficacy of the combination in the indications requested as it stands.

**Clinical efficacy conclusion**

Overall the data presented (both study and bibliographic) by the applicant generally demonstrates the efficacy of the actives ibuprofen and pseudoephedrine hydrochloride separately and in combination for the indications proposed.

**IV.5 Clinical safety**

The applicant has adequately summarised the bibliographic data available on the safety of pseudoephedrine hydrochloride as a lone active. The data is adequate for adults and children. It adequately discusses overdose, pregnancy and lactation.

The applicant has provided a comprehensive and up to date summary of the available literature data on the combination of the actives.

**IV.6 Risk Management Plan (RMP) and Pharmacovigilance System**

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 Ibuprofen/Pseudoephedrine hydrochloride Capsules.

**A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:**

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine Risk Minimisation Measures</th>
<th>Additional Risk Minimisation Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity Reactions (including severe skin reactions such as Exfoliative dermatitis, Stevens-Johnson syndrome and Toxic epidermal necrosis, and including bronchospasm particularly in those patients with a history of bronchial asthma or allergic disease)</td>
<td>SPC Section 4.3 Contraindications, SPC Section 4.4 Special Warnings and Precautions for Use, SPC Section 4.8 Undesirable Effects, and PIL.</td>
<td>None.</td>
</tr>
<tr>
<td>Gastrointestinal Ulceration and Haemorrhage</td>
<td>SPC Section 4.3 Contraindications, SPC Section 4.4 Special Warnings and Precautions for Use, SPC Section 4.8 Undesirable Effects, and PIL.</td>
<td>None.</td>
</tr>
<tr>
<td>Cardiovascular Thrombotic and Ischaemic Events (including MI and stroke)</td>
<td>SPC Section 4.4 Special Warnings and Precautions for Use and PIL.</td>
<td>None.</td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>SPC Section 4.3 Contraindications, SPC Section 4.4 Special Warnings and Precautions for Use, SPC Section 4.8 Undesirable Effects and PIL.</td>
<td>None.</td>
</tr>
<tr>
<td>Foetus PDA Premature Closure (use in third trimester of pregnancy) or Gastrochisis (use during pregnancy)</td>
<td>SPC Section 4.3 Contraindications, SPC Section 4.6 Fertility, Pregnancy and Lactation and PIL.</td>
<td>None.</td>
</tr>
</tbody>
</table>
Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

In addition, the applicant is participating in a study initiated by the French medicines regulatory authority to further characterise the vaso-constrictive effects of pseudoephedrine hydrochloride. The applicant has presented details of this study in the appropriate sections of the pharmacovigilance plan, including in Annex 5 – synopsis of ongoing and completed pharmacoepidemiological study programme. The RMS considers that routine pharmacovigilance and the applicant’s involvement in the ongoing post-authorisation study are sufficient to identify and characterise the risks of the product. The RMS also considered that routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V User consultation

For Ibuprofen/ Pseudoephedrine hydrochloride Pfizer 200 mg/ 30 mg Capsules (PL 00165/0389; UK/H/5671/001/DC):

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.

For RobiCold Cold & Flu Relief 200 mg / 30 mg Soft Capsules (PL 00165/0388; UK/H/5670/001/DC):

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Ibuprofen/ Pseudoephedrine hydrochloride Pfizer 200 mg/ 30 mg Capsules (PL 00165/0389; UK/H/5671/001/DC). The bridging report submitted by the applicant is acceptable.
VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ibuprofen and pseudoephedrine hydrochloride separately and in combination is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

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

The following text is the approved label text for Ibuprofen/Pseudoephedrine hydrochloride Pfizer 200 mg/30mg Capsules; no label mock-ups has been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained. The UK label mock-ups for RobiCold Cold & Flu Relief 200 mg / 30 mg Soft Capsules (PL 00165/0388; UK/H/5670/001/E/001) are provided in Annex 1 below.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING |
| Carton |

| 1. NAME OF THE MEDICINAL PRODUCT |
| Ibuprofen/Pseudoephedrine hydrochloride Pfizer 200mg/30mg Capsules |

| 2. STATEMENT OF ACTIVE SUBSTANCE(S) |
| Each capsule contains Ibuprofen 200 mg and Pseudoephedrine hydrochloride 30 mg. |

| 3. LIST OF EXCIPIENTS |
| Also Contains: Sorbitol (E 420), soya lecithin and potassium—see package leaflet for further information |

| 4. PHARMACEUTICAL FORM AND CONTENTS |
| 2 capsules |
| 4 capsules |
| 8 capsules |
| 10 capsules |
| 12 capsules |
| 16 capsules |
| 20 capsules |
| 24 capsules |

| 5. METHOD AND ROUTE(S) OF ADMINISTRATION |
| For oral use. For short term use only. |
| Read the package leaflet before use. |

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

| 7. OTHER SPECIAL WARNING(S), IF NECESSARY |
| Read the enclosed leaflet before taking this product. |
| Do not take if you have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding; are allergic to ibuprofen or any other ingredient of the product; aspirin or other related painkillers; are taking other NSAID painkillers, or aspirin with a daily dose above 75mg |
Speak to a pharmacist or your doctor before taking if you have or have had asthma, diabetes, high cholesterol, high blood pressure, a stroke, heart, liver, kidney or bowel problems, are a smoker, are pregnant.

If symptoms persist or worsen, consult your doctor.

Do not exceed the stated dose.

8. EXPIRY DATE

EXP. Month/Year

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Keep all medicines out of the sight and reach of children.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Consumer Healthcare Ltd
Ramsgate Road
Sandwich
Kent, CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 00165/0389

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot: XXXX

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

NEW Ibuprofen/Pseudoephedrine hydrochloride Pfizer 200mg/30mg Capsules
For fast relief of symptoms associated with the common cold, flu and sinus.
Gets to work faster for pain relief associated with the common cold, flu and sinus.*
* Compared to standard ibuprofen and pseudoephedrine combination tablets.

Ibuprofen relieves headache and fever, minor aches and pains and eases sore throats.
Pseudoephedrine hydrochloride, a decongestant, relieves blocked noses and sinuses.

Adults: older people and adolescents over 15 years of age: 1 to 2 capsules with a drink of water every 4 to 6 hours. Do not take more than 6 capsules in a 24 hour period.

Not suitable for children under 15 years.

<table>
<thead>
<tr>
<th>16. INFORMATION IN BRAILLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen/ Pseudoephedrine hydrochloride Pfizer 200mg/30mg Capsules</td>
</tr>
</tbody>
</table>

| MINIMUM PARTICULARS TO APPEAR ON BISTERS OR STRIPS |
| [Blisters] |

| 1. NAME OF THE MEDICINAL PRODUCT |
| Ibuprofen/ Pseudoephedrine hydrochloride Pfizer 200mg/30mg Capsules |

| 2. NAME OF THE MARKETING AUTHORISATION HOLDER |
| Pfizer Consumer Healthcare Ltd |

| 3. EXPIRY DATE |
| EXP. (month/year) |

| 4. BATCH NUMBER<, DONATION AND PRODUCT CODES> |
| Lot: XXXX |

| 5. OTHER |
Please note the below update only concerns procedure UK/H/5670/001/DC.

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

The following table lists non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post authorisation changes that have been made to this Marketing Authorisation.

<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</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) To update the invented name of the medicinal product in Romania from 'Advil Sinus si Raceala' to 'Robicold Sinus &amp; Raceala' and 2) To update the invented name in the United Kingdom from, 'RobiCold Cold &amp; Flu Relief 200mg/30mg Liquid Capsules' to 'RobiCold Cold &amp; Flu Relief 200 mg/30mg Soft Capsules'. SmPC and PIL updated.</td>
<td>UK/H/5670/001/IB/002/G</td>
<td>SmPC and PIL</td>
<td>09/05/2016</td>
<td>09/08/2016</td>
<td>Approval</td>
<td>No</td>
</tr>
<tr>
<td>To extend the shelf life of the finished product to 3 years. To change the finished product storage conditions 'store below 25°C'. The product information has been updated accordingly.</td>
<td>UK/H/5670/001/IB/005/G</td>
<td>SmPC</td>
<td>20/07/2017</td>
<td>07/09/2017</td>
<td>Approval</td>
<td>No</td>
</tr>
<tr>
<td>To update sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 6.1 of the Summary of Product Characteristics (SmPC) following comments received during the Repeat Use Mutual Recognition Procedure (MRP) UK/H/5670/001/E/001. Consequentially, the label and leaflet have been updated</td>
<td>UK/H/5670/001/IB/004</td>
<td>SmPC, PIL and labelling</td>
<td>04/05/2017</td>
<td>26/10/2017</td>
<td>Approval</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL – 00165/0388-0008

Product: RobiCold Cold & Flu Relief 200 mg / 30 mg Soft Capsules

Marketing Authorisation Holder: Pfizer Consumer Healthcare Ltd

Active Ingredient: Ibuprofen and pseudoephedrine

Reason:
To update sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 6.1 of the Summary of Product Characteristics (SmPC) following comments received during the Repeat Use Mutual Recognition Procedure (MRP) UK/H/5670/001/E/001. Consequentially, the label and leaflet have been updated.

Supporting evidence
The applicant has submitted updated SmPC, PIL and labelling.

Evaluation
The amended SmPC, PIL and labelling are satisfactory.

Conclusion
The updated SmPC, PIL and labelling have been incorporated into this Marketing Authorisation. The proposed changes are acceptable.

Decision: Grant
Date: 26 October 2017
The current approved UK labelling is presented below: