Public Assessment Report

Decentralised Procedure

Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets

(Ibuprofen and phenylephrine hydrochloride)

Procedure No: UK/H/5494/001/DC

UK Licence No: PL 11204/0297

STADA Arzneimittel AG
LAY SUMMARY

Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets
(ibuprofen and phenylephrine hydrochloride, film-coated tablets, 200mg/5mg)

This is a summary of the Public Assessment Report (PAR) for Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets (PL 11204/0297; UK/H/5494/001/DC). It explains how Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets.

For practical information about using Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets and what are they used for?
Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets is a medicine with ‘well established use’. This means that the medicinal use of the active substances ibuprofen and phenylephrine hydrochloride is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

The active substances ibuprofen and phenylephrine hydrochloride are effective in relieving the symptoms associated with colds and flu, including relief of aches and pains, sore throats, headache, nasal congestion (blocked nose) and lowering temperature.

How do Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets work?
Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets contain the active ingredients ibuprofen and phenylephrine hydrochloride.

Ibuprofen belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs) and is effective against aches and pains (including headache), swelling and can also reduce a fever. Phenylephrine hydrochloride is a nasal decongestant which works by reducing the swelling of the passages of the nose, relieves nasal congestion and reduces the pressure which may cause a headache.

How are Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets used?
The pharmaceutical form of Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets is a film-coated tablet and the route of administration is oral.

This medicine must always be taken exactly as described in the package leaflet or as the patient’s doctor has told them. The patient must check with their doctor or pharmacist if they are not sure.

The dosage for adults, the elderly and children over 12 years of age is two tablets to be taken every 8 hours. The patient must leave at least 4 hours between doses and must not exceed 6 tablets in any 24 hour period.

The tablets must be swallowed whole with water. It is important to drink plenty of fluids when suffering from colds and flu.

This medicine is for short-term use only. The patient should take the lowest dose for the shortest time necessary to relieve their symptoms. The patient must not take this medicine for longer than 10 days.
This medicine must not be given to children under 12 years of age.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can be obtained without a prescription.

What benefits of Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets have been shown in studies?
As ibuprofen and phenylephrine hydrochloride are well-known substances, and their use in relieving the symptoms associated with colds and flu, including relief of aches and pains, sore throats, headache, nasal congestion (blocked nose) and lowering of temperature is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the use of ibuprofen and phenylephrine hydrochloride in relieving the symptoms associated with colds and flu, including relief of aches and pains, sore throats, headache, nasal congestion (blocked nose) and lowering of temperature.

In addition, the company (STADA Arzneimittel AG) undertook a bioequivalence study to bridge their product to the information found in the bibliographic sources relating to the currently approved ibuprofen and phenylephrine hydrochloride-containing products. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

It was concluded from the study that Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets are bioequivalent to another ibuprofen and phenylephrine hydrochloride-containing product already on the market, Nurofen Cold & Flu relief 200mg/5mg Tablets.

What are the possible side effects of Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets?
For the full list of all side effects reported with Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets, see section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why were Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets approved?
The use of ibuprofen and phenylephrine hydrochloride in relieving the symptoms associated with colds and flu, including relief of aches and pains, sore throats, headache, nasal congestion (blocked nose) and lowering of temperature 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 and Phenylephrine hydrochloride 200mg/5mg film coated tablets outweigh the risks and the grant of a marketing authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets?
A risk management plan has been developed to ensure that Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets, including 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 and Phenylephrine hydrochloride 200mg/5mg film coated tablets

The marketing authorisation for Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets was granted in the UK on 22 December 2014.

The full PAR for Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets follows this summary.

For more information about use of Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2015.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted STADA Arzneimittel AG a Marketing Authorisation for the medicinal product Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets (PL 11204/0297; UK/H/5494/001/DC) on 22 December 2014. The product is a pharmacy (P) medicine indicated for the relief of symptoms of colds and flu with associated congestion, including aches and pains, headache, fever, sore throat, blocked nose and sinuses.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Germany as Concerned Member State (CMS). The applicant subsequently withdrew the application in Germany during the procedure, leaving no CMS. The application was submitted 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.

Ibuprofen is a propionic acid derivative non-steroidal anti-inflammatory drug (NSAID) that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

The therapeutic effect of ibuprofen in symptoms relating to the common cold and influenza has a duration of up to 8 hours.

Phenylephrine hydrochloride is a post-synaptic alpha-receptor agonist with low cardioselective beta-receptor affinity and minimal central stimulant activity. It is a recognised decongestant and acts by vasoconstriction to reduce oedema and nasal swelling.

Bibliographic data on ibuprofen and phenylephrine hydrochloride have been submitted to support this application. No new non-clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing active ingredients of well-established use.

In addition to the submission of published non-clinical and clinical references the applicant has also performed a bioequivalence study (open-label, single-dose, randomised, two-way, cross-over study) to bridge their product to the information found in the bibliographic sources relating to a currently approved ibuprofen and phenylephrine hydrochloride containing product, Nurofen Cold & Flu Relief 200mg/5mg tablets (Reckitt Benckiser Healthcare (UK) Ltd, UK). The applicant has stated that the bioequivalence study was conducted in compliance with Good Clinical practice (GCP).

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.
II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains 200mg ibuprofen and 5 mg phenylephrine hydrochloride. Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, sodium starch glycolate, hypromellose, sodium stearyl fumarate, purified water and the film coat Opadry 200 white 200F280000 (consisting of polyvinyl alcohol, talc, macrogol, titanium dioxide, methacrylic acid copolymer, sodium bicarbonate and purified water). The finished product is packed into polyvinyl chloride (PVC)/polyethylene (PE)/polyvinylidene chloride (PVdC)/aluminium blisters in pack sizes of 12, 16, 20 and 24 tablets. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
1. Ibuprofen
INN: Ibuprofen
Chemical Name: α-methyl-1-(2-methylpropyl)-benzeneacetic acid; p-Isobutylhydrotropic acid; 2-(4-Isobutylphenyl) propionic acid

Structure:

Molecular formula: C₁₃H₁₈O₂
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.

2. Phenylephrine hydrochloride
INN: Phenylephrine hydrochloride
Chemical Name: (1R)-1-(3-Hydroxyphenyl)-2-(methylamino)ethanol hydrochloride.

Structure:

Molecular formula: C₀H₁₄ClNO₂
Molecular weight: 203.7
Appearance: White or almost white, crystalline powder.
Solubility: Freely soluble in water and in ethanol (96 per cent).

Phenylephrine hydrochloride is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance, phenylephrine 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, film-coated tablets containing 200mg ibuprofen and 5 mg phenylephrine hydrochloride per film-coated tablet.

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the film-coat Opadry 200 white 200F280000 which is controlled to a suitable in-house specification. In addition, all colourings are stated to comply with EU approved specifications for colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of this product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

Finished Product Specifications
The finished product specification proposed is 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 finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months with the storage conditions ‘Do not store above 30°C.’

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

II.5 Summaries of Product Characteristics (SmPC), Patient Information Leaflets (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 and Phenylephrine hydrochloride 200mg/5mg film coated tablets. No label mock-ups have 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:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING TEXT FOR ALL PACK SIZES

1. NAME OF THE MEDICINAL PRODUCT
   Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets
   Ibuprofen/Phenylephrine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)
   Each film coated tablet contains the active substances:
   200.0 mg Ibuprofen
   5.0 mg Phenylephrine hydrochloride

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
   12 tablets
   16 tablets
   20 tablets
   24 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
   Oral use
   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

8. EXPIRY DATE
   EXP

9. SPECIAL STORAGE CONDITIONS
   Store in the original package 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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
   STADA Arneplit AG
   Stadastr. 2-8
   61118 Bad Vilbel
   Germany

12. MARKETING AUTHORISATION NUMBER(S)
   PL 11204/0297
13. BATCH NUMBER
Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE
Oral use. Take as directed by a doctor.
Read the package leaflet before use.

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT
Ibuprofen and Phenylephrine 200mg/5mg film coated tablets
Ibuprofen/Phenylephrine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER
STADA Arzneimittel AG

3. EXPIRY DATE
EXP

4. BATCH NUMBER
Batch

5. OTHER
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen and phenylephrine 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 environmental risk assessment (ERA) for ibuprofen has been provided, based on published literature.
The predicted environmental concentration in surface water (PEC_{surface_water}) is calculated as 12µg/L, based on a daily dose of 2400mg and default values in the guideline equation.
Phase II Tier A information is provided for ready biodegradability, aerobic and anaerobic transformation in aquatic sediment systems, adsorption coefficient, activated sludge respiration inhibition test and aquatic effect studies (in fish, crustacea and algae). Although a number of the published studies used alternative methodology to that recommended in the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2*), the results were often consistent and have been discussed by the expert.
Predicted no-effect concentrations (PNECs) were calculated and outcome of Tier A fate and effects analysis discussed; effects on sediment organisms were investigated in Tier B.
PES_{surface_water} was also refined, taking into account the performance of sewage treatment plants. The revised PEC/PNEC ratios did not alter the outcome of the Tier A fate and effects analysis.

The overall conclusion is that ibuprofen will not pose a risk to the environment.

The absence of an environmental risk assessment for phenylephrine hydrochloride has been justified based on data demonstrating a decrease in sales for the monoprodut and combination products.

The proposed product is intended to replace the use of similar products already on the market. The conclusion that ibuprofen will not pose a risk to the environment is acceptable. The use of phenylephrine hydrochloride appears to be decreasing overall and an ERA has not been provided. In addition, the proposed product is intended to replace the use of similar products already on the market and consequently no additional risk is likely to occur to the environment from use of this product.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that this is a bibliographic application for a product containing active ingredients of well-established use.

There are no objections to the approval of this application from a non-clinical viewpoint.
IV CLINICAL ASPECTS

IV.1 Introduction
One bioequivalence study was submitted to support this application. The study was designed to demonstrate that the test product, Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets (STADA Arzneimittel AG) was bioequivalent to the currently approved ibuprofen and phenylephrine hydrochloride containing product, Nurofen Cold & Flu Relief 200mg/5mg tablets (Reckitt Benckiser Healthcare (UK) Ltd, UK).

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

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

IV.2 Pharmacokinetics
The applicant has submitted the following study:

STUDY
An open label, randomised, single-dose, two-stage crossover study to compare the pharmacokinetics of the applicant’s test product Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets (STADA Arzneimittel AG) versus the market standard reference product, Nurofen Cold & Flu Relief 200mg/5mg tablets (Reckitt Benckiser Healthcare (UK) Ltd, UK), in healthy adult subjects under fasting conditions.

The primary objective of the study was to assess bioequivalence of the test product compared to the market standard reference product. In order to investigate the bioequivalence of the test and reference product, a two-stage study design was chosen. Based on the results after stage 1, the study could have been stopped or continued with stage 2.

Each subject was randomised to receive an oral single dose of the test product (one film-coated tablet containing 200 mg ibuprofen and 5 mg phenylephrine hydrochloride) or the reference product (one film-coated tablet containing 200 mg ibuprofen and 5 mg phenylephrine hydrochloride) administered with 240 ml of tap water on two single occasions under fasting conditions.

Blood samples were collected before and up to and including 12 hours post-dose. The washout period between treatment phases was at least 4 days. The pharmacokinetic results for the active metabolites S-ibuprofen and phenylephrine are presented below (94.12% confidence intervals (first stage), primary endpoints AUC_{0-t} and C_{max}):

<table>
<thead>
<tr>
<th>Variable</th>
<th>Method</th>
<th>Point Estimator</th>
<th>Confidence Intervals</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-t}</td>
<td>ANOVA-log</td>
<td>100.16%</td>
<td>97.81% - 102.57%</td>
<td>5.15%</td>
</tr>
<tr>
<td>C_{max}</td>
<td>ANOVA-log</td>
<td>97.93%</td>
<td>92.63% - 103.53%</td>
<td>12.11%</td>
</tr>
</tbody>
</table>

From the data provided, it is accepted that the test product Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets are bioequivalent to the reference product Nurofen Cold & Flu Relief.
200mg/5mg tablets (Reckitt Benckiser Healthcare (UK) Ltd, UK) in terms of rate and extent of absorption for both analytes S-ibuprofen and phenylephrine after the first stage. Therefore the second stage of the study was not performed as per the definition in the study protocol. As a consequence, it can be concluded that the clinical data for the already approved Nurofen Cold & Flu Relief 200mg/5mg tablets are directly applicable to the applicant’s Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets with regard to efficacy, and the bridging study is accepted.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type. The clinical efficacy of ibuprofen and phenylephrine hydrochloride is well-established. Efficacy is adequately reviewed in the clinical overview.

IV.5 Clinical safety
No new safety data were submitted and none were required for this bibliographic application. Safety is adequately reviewed in the clinical overview. The safety profiles of ibuprofen and phenylephrine hydrochloride are well-known.

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 and Phenylephrine hydrochloride 200mg/5mg film coated tablets.

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

Summary table of safety concerns as approved in the RMP:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Ibuprofen:</th>
</tr>
</thead>
<tbody>
<tr>
<td>G I bleeding, ulceration or perforation</td>
<td></td>
</tr>
<tr>
<td>Serious skin reactions such as Steven-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN)</td>
<td></td>
</tr>
<tr>
<td>Arterial thrombotic events</td>
<td></td>
</tr>
<tr>
<td>Renal impairment</td>
<td></td>
</tr>
<tr>
<td>Allergic reactions in response to aspirin or other NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Bronchospasm in patients with a history of bronchial asthma or allergic disease</td>
<td></td>
</tr>
<tr>
<td>Hepatic disorders</td>
<td></td>
</tr>
<tr>
<td>Premature closure of the fetal ductus arteriosus</td>
<td></td>
</tr>
<tr>
<td>Phenylephrine:</td>
<td></td>
</tr>
<tr>
<td>Use during pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
<th>Ibuprofen:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptic meningitis in patients with SLE and mixed connective tissue disease</td>
<td></td>
</tr>
<tr>
<td>Skin reactions with eosinophilia and systemic symptoms (DRESS)</td>
<td></td>
</tr>
<tr>
<td>Impaired female fertility</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Missing information</th>
<th>Ibuprofen/phenylephrine:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Exposure during lactation</td>
<td></td>
</tr>
<tr>
<td>Exposure in children below 12 years of age</td>
<td></td>
</tr>
</tbody>
</table>
Summary table of risk minimisation measures as approved in the RMP:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Gastrointestinal bleeding, ulceration or perforation| Included in SPC section(s)  
- 4.4 Special warnings and precautions for use  
- 4.8 Undesirable effects  
Included in PIL. Described in lay terms and distributed with each package. | NA                                   |
| Serious skin reactions such as Steven-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN) | Included in SPC section(s)  
- 4.4 Special warnings and precautions for use  
- 4.8 Undesirable effects  
Included in PIL. Described in lay terms and distributed with each package. | NA                                   |
| Arterial thrombotic events                          | Included in SPC section(s)  
- 4.4 Special warnings and precautions for use  
- 4.8 Undesirable effects  
Included in PIL. Described in lay terms and distributed with each package. | NA                                   |
| Renal impairment                                    | Included in SPC section(s)  
- 4.3 Contraindications  
- 4.4 Special warnings and precautions for use  
- 4.8 Undesirable effects  
Included in PIL. Described in lay terms and distributed with each package. | NA                                   |
| Allergic reactions in response to aspirin or other NSAIDs | Included in SPC section(s)  
- 4.3 Contraindications  
Included in PIL. Described in lay terms and distributed with each package. | NA                                   |
<table>
<thead>
<tr>
<th>Condition/Scenario</th>
<th>Details</th>
<th>NA</th>
</tr>
</thead>
</table>
| Bronchospasm in patients with a history of bronchial asthma or allergic disease | Included in SPC section(s)  
- 4.4 Special warnings and precautions for use  
- 4.8 Undesirable effects  
  Included in PIL. Described in lay terms and distributed with each package. | NA |
| Hepatic disorders                                      | Included in SPC section(s)  
- 4.3 Contraindications  
- 4.4 Special warnings and precautions for use  
- 4.8 Undesirable effects  
  Included in PIL. Described in lay terms and distributed with each package. | NA |
| Premature closure of the fetal ductus arteriosus       | Included in SPC section(s)  
- 4.3 Contraindications  
- 4.6 Fertility, pregnancy and lactation  
  Included in PIL. Described in lay terms and distributed with each package. | NA |
| Use during pregnancy                                   | Included in SPC section(s)  
- 4.6 Fertility, pregnancy and lactation  
  Included in PIL. Described in lay terms and distributed with each package. | NA |
| **Important potential risks**                          |                                                                         |    |
| Aseptic meningitis in patients with SLE and mixed connective tissue disease | Included in SPC section(s)  
- 4.4 Special warnings and precautions for use  
- 4.8 Undesirable effects  
  Included in PIL. Described in lay terms and distributed with each package. | NA |
| Skin reactions with eosinophilia and systemic symptoms (DRESS) | Currently available data do not support the need for risk minimisation measures. | NA |
The RMP is considered to accurately reflect the safety concerns associated with this product and is considered acceptable.

IV.7 Discussion on the clinical aspects
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

The bibliographic data submitted for this application does support the claim of well-established use for the sought indication of:
‘The relief of symptoms of cold and flu with associated congestion, including aches and pains, headache, fever, sore throat, blocked nose and sinuses.’ in the target population.

The applicant has also performed a bioequivalence study effectively bridging Ibuprofen and Phenylephrine hydrochloride 200mg/5mg film coated tablets to the information found in the bibliographic sources relating to the currently approved Nurofen Cold & Flu Relief 200mg/5mg tablets (Reckitt Benckiser Healthcare (UK) Ltd, UK).
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, as amended. 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. Extensive clinical experience with ibuprofen and phenylephrine hydrochloride is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk is, therefore, considered to be positive.