Public Assessment Report

UKPAR

Ibuprofen and Pseudoephedrine hydrochloride Farmalider
200 mg/ 30 mg/10 ml oral suspension

(ibuprofen and pseudoephedrine hydrochloride)

UK Licence Number: PL 35667/0020

Farmalider, S.A.
LAY SUMMARY

Ibuprofen and Pseudoephedrine hydrochloride Farmalider 200 mg/ 30 mg/10 ml oral suspension

This is a summary of the Public Assessment Report (PAR) for Ibuprofen and Pseudoephedrine hydrochloride Farmalider 200 mg/ 30 mg/10 ml oral suspension (PL 35667/0020). It explains how Ibuprofen and Pseudoephedrine hydrochloride Farmalider 200 mg/ 30 mg/10 ml oral suspension was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Ibuprofen and Pseudoephedrine hydrochloride Farmalider 200 mg/ 30 mg/10 ml oral suspension.

This product will be referred to as Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension throughout the remainder of this public assessment report.

For practical information about using Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension, patients should read the package leaflet or contact their doctor or pharmacist.

What is Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension and what is it used for?

Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension is a medicine with ‘well established use’. This means that the medicinal use of the active substances, of Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension, both individually and in combination are well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension is indicated for adults and adolescents aged 12 years and above for the relief of symptoms of cold and flu with associated pain, fever, congestion and blocked nose.

How does Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension work?

Ibuprofen and Pseudoephedrine hydrochloride Farmalider 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 hydrochloride belongs to a group of drugs called vasoconstrictors, which act on the blood vessels in the nose to relieve nasal congestion.

How is Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension used?

The pharmaceutical form of this medicine is an oral suspension and the route of administration is by mouth (oral).

The patient should always take this medicine exactly as the patient’s doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

Before measuring the dose shake the bottle well until the sediment in the bottle is completely dispersed. An oral dosing syringe is provided to ensure accurate dose measurement.

The recommended dose in adults and adolescents aged 12 years and above:

Depending on the severity of the symptoms 10 ml to 20 ml every six to eight hours. Never exceed the maximum daily dose of 60 ml.
• do not take more than the stated dose
• the medicine should be used for shortest time possible at the lowest dose to relieve the symptoms
• this medicine should not be given to children under 12 years of age
• doses should usually be given every 6 to 8 hours as required. Leave at least 4 hours between doses.

**Use in children and adolescents:**
This medicine is not recommended for use in children under 12 years of age.

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

This medicine can be obtained without a prescription.

**What benefits of Ibuprofen and Pseudoephedrine hydrochloride Farmalider 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 flu with associated congestion, including aches and pains, headache, sore throat and blocked nose 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, the Marketing Authorisation Holder (MAH) Farmalider, S.A., undertook a bioequivalence study to bridge their product to the information found in bibliographic sources 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.

It was concluded from the study that Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension is bioequivalent to another already approved similar medicinal product which contains the active substance ibuprofen; Junifen (20mg/mL ibuprofen oral suspension – Reckitt Benckiser healthcare SA Spain) and as a single active substance in Sudafed Decongestant Liquid (6mg/mL pseudoephedrine hydrochloride oral solution – McNeil Limited UK).

**What are the possible side effects of Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension?**
Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common side effects with Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension (which may affect up to 1 in 10 people) are:
• inflammation of stomach or intestine, sometimes with blood loss leading to anaemia
• indigestion, stomach-ache, loss of appetite
• feeling and being sick
• diarrhoea, wind or constipation

For the full list of all side effects reported with Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension, see section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet.
Why is Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension approved?
The MHRA decided that the benefits of Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension are greater than its risks and recommended that it was approved for use.

What measures are being taken to ensure the safe and effective use of Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension?
A risk management plan (RMP) has been developed to ensure that Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension is 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 Pseudoephedrine hydrochloride Farmalider oral suspension 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 and Pseudoephedrine hydrochloride Farmalider oral suspension
The Marketing Authorisation for Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension was granted on 18 June 2018.

The full PAR for Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension follows this summary.

For more information about treatment with Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2018.
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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 the Marketing Authorisation Holder (MAH), Farmalider, S.A., a marketing authorisation for the medicinal product Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension (PL 35667/0020). This pharmacy (P) medicine is indicated in adults and adolescents over 12 years of age for the relief of symptoms of cold and flu with associated pain, fever, congestion and blocked nose.

This application was submitted as an abridged national application according to 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 and Pseudoephedrine hydrochloride Farmalider oral suspension is a medicine consisting of a combination of two active substances; ibuprofen and pseudoephedrine hydrochloride.

Pseudoephedrine is a sympathomimetic agent with direct and indirect effects on adrenergic receptors. It has alpha and beta stimulant adrenergic stimulant activity and some stimulant effect on the central nervous system. The sympathomimetic effect of pseudoephedrine produces vasoconstriction which relieves nasal congestion.

Ibuprofen is an anti-inflammatory analgesic and antipyretic drug belonging to the group of non-steroidal anti-inflammatory drugs. In humans, it has been shown to be effective in reducing the symptoms (pain, fever and swelling) associated with inflammation and influenza. The therapeutic effects of the drug are the result of an inhibitory activity on the prostaglandin synthesis.

Bibliographic data on ibuprofen and pseudoephedrine 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 substances of well-established use.

In addition to the submission of published non-clinical and clinical references the MAH has also performed a bioequivalence study to evaluate the bioavailability between 200 mg/30 mg of ibuprofen/pseudoephedrine hydrochloride (20 mg/ml / 3 mg/ml oral suspension) and 200 mg of Junifen 20 mg/ml oral suspension orange flavour (ibuprofen) in addition to 30 mg of Sudafed decongestant liquid (pseudoephedrine) given concomitantly. The applicant has stated that the bioequivalence study was conducted in accordance 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, assembly and batch release of this product.

For manufacturing sites within the Community, the MHRA 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.

No new or unexpected safety concerns arose during the review of information provided by the MAH and it was, therefore, judged that the benefits of taking Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension outweigh the risks and a Marketing Authorisation was granted on 18 June 2018.
II QUALITY ASPECTS

II.1 Introduction
Each ml of oral suspension contains:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>20 mg</td>
</tr>
<tr>
<td>Pseudoephedrine hydrochloride</td>
<td>3 mg</td>
</tr>
<tr>
<td>Excipients with known effect:</td>
<td></td>
</tr>
<tr>
<td>Glycerol (E-422)</td>
<td>50 mg</td>
</tr>
<tr>
<td>Maltitol</td>
<td>500 mg</td>
</tr>
<tr>
<td>Sodium</td>
<td>2.68 mg</td>
</tr>
</tbody>
</table>

Other ingredients consist of the pharmaceutical excipients sodium benzoate, anhydrous citric acid, sodium citrate, saccharin sodium, sodium chloride, hypromellose, xanthan gum, liquid maltitol, thaumatin (E-957), orange flavour (contains butylated hydroxyanisole (E-320), alpha-tocopherol (E307)) and purified water.

The finished product is available in amber coloured polyethylene terephthalate bottles of 150 ml and 200 ml, with child-resistant closure. The packaging also contains a 5 ml dosing syringe (graduated in millilitres) to ensure accuracy. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for the packaging components.

II.2 Drug Substances

1. Ibuprofen
   INN: Ibuprofen
   Chemical Name: (2RS)-2-[4-methylpropyl]phenyl]propanoic acid.

   Structure:
   ![Ibuprofen Structure](image)

   Molecular formula: \(C_{13}H_{18}O_2\)
   Molecular weight: 206.3
   Appearance: White or almost white, crystalline powder
   Solubility: Practically insoluble in water, freely soluble in acetone, in methanol and in dichloromethane. 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 an EDQM Certificate of Suitability.
2. **Pseudoephedrine hydrochloride**

INN: Pseudoephedrine hydrochloride

Chemical Name: (1S,2S)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride.

Structure:

![Structure of Pseudoephedrine hydrochloride](image)

Molecular formula: \( \text{C}_{10}\text{H}_{16}\text{ClN} \)

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 dichloromethane.

Pseudoephedrine hydrochloride is the subject of a European Pharmacopoeia monograph. All aspects of the manufacture and control of the active substance, ibuprofen, are covered by an EDQM Certificate of Suitability.

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

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

II.3. **Medicinal Product**

**Pharmaceutical Development**

The objective of the development programme was to formulate a safe, efficacious, oral suspension with combined action of the active ingredients ibuprofen and pseudoephedrine hydrochloride.

A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity profiles have been provided for the proposed product and already approved similar products (Junifen 20 mg/ml oral suspension and Sudafed decongestant liquid) combined action of the active ingredients ibuprofen and pseudoephedrine hydrochloride, similarity, has been confirmed between the two.

All excipients comply with their respective monographs. Thaumatin (E-957) and the individual constituents of the orange flavouring (butylated hydroxyanisole (E-320), alpha-tocopherol (E307)) comply with their in-house specifications and all other excipients comply with the European Pharmacopoeia monographs. Suitable batch analysis data have been provided for each excipient.

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

This product does not contain or consist of genetically modified organisms (GMO).
Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on commercial scale batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. 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 for the unopened product, with the in-use storage conditions ‘after the first opening the suspension is stable for 3 months’.

A suitable post approval stability commitment to continue stability testing on batches of finished product has been provided.

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

III  NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacological, pharmacokinetic and toxicological properties of ibuprofen and pseudoephedrine hydrochloride have been well characterised. New non-clinical studies are not required and the applicant has not conducted any. A literature review is, therefore, appropriate. The Applicant has provided an adequate discussion of the literature on the pharmacology, pharmacokinetics and toxicity of ibuprofen and pseudoephedrine hydrochloride.

The MAH’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
The pharmacology of the active substances, ibuprofen and pseudoephedrine hydrochloride is adequately discussed in the MAH’s non-clinical overview and is briefly summarised below.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), indicated for the treatment of pain, fever and inflammation. Painful stimuli and cytokines (including TNF-α, IL-8 and IL-1), results in the release of bradykinin, and subsequently prostaglandin, which appears to sensitise pain receptors by lowering the threshold of C-fibre nociceptors. Like other NSAIDs, ibuprofen reduces prostaglandin synthesis through inhibition of the cyclooxygenase (COX) enzyme, resulting in analgesia.

Pseudoephedrine is a stereoisomer of ephedrine, and has similar vasoconstrictive action, but fewer central nervous system effects. Pseudoephedrine is an α- and β-adrenergic receptor agonist, which is used to relieve nasal and sinus congestion commonly associated with colds or allergies. In contrast to nasal preparations, such as oxymetazoline, oral pseudoephedrine does not lead to rebound congestion.

• Physical chemistry
III.3 Pharmacodynamics

Primary Pharmacodynamics

Ibuprofen

Ibuprofen is a propionic acid derivative, with analgesic, antipyretic and anti-inflammatory mechanisms of action. Ibuprofen non-selectively inhibits COX-1 and 2 enzymes, involved in the conversion of arachidonic acid into various eicosanoids including thromboxane and prostaglandins. COX-1 and 2 metabolise arachidonic acid in identical fashion to form the labile endoperoxide PGH2, which is subsequently metabolised by various synthase enzymes to the physiologically important prostaglandins, TXA2, PGI2, PGE2, PGF2α and PGD2. Prostaglandins, especially PGE2 and PGI, are potent vasodilators promoting the increased vascular permeability and oedema formation which occurs during acute inflammation. NSAID-mediated fever suppression is believed to occur primarily through the suppression of PGE2, and in inflammatory pain, prostaglandins, in particular PGE2 and PGI2, are believed to sensitise the free ends of neurons. The therapeutic effects of ibuprofen are largely through COX-2 inhibition, whereas COX-1 inhibition is believed to be linked to the well-known dose-dependent gastrointestinal side effects, such as ulceration, partly a result of increased gastric secretion.
There is non-clinical evidence of numerous other anti-inflammatory mechanisms of NSAIDs, including ibuprofen. However, whether these mechanisms have importance in the clinical setting is currently not known. In human and rat leukocytes, ibuprofen inhibits stimulation and chemotaxis, thus reducing accumulation at inflammatory sites. Ibuprofen has been shown to inhibit the release of reactive oxygen species, which may be partially responsible for inflammation-induced tissue damage. In addition, in vitro studies have shown that ibuprofen can inhibit induced histamine release from mast cells.

Pseudoephedrine

Pseudoephedrine is a sympathomimetic amine, with agonistic activity at both α- and β-adrenergic receptors. Pseudoephedrine is less potent than ephedrine, and therefore has less unwanted side effects such as increases in blood pressure and CNS excitatory effects. The action of pseudoephedrine-mediated agonism on α1-adrenergic receptors in the respiratory tract mucosa leads vasoconstriction, and a subsequent decongestant effect. Agonism of the β2-adrenergic receptors results in bronchial smooth muscle relaxation, thereby reducing congestion and breathing difficulties. Pseudoephedrine also has some agonist activity at the β1-adrenergic receptors, which may lead to increased systolic blood pressure (see section III.2).

Conclusion

The pharmacology of ibuprofen and pseudoephedrine is well known and described in the literature. The Marketing Authorisation Holder (MAH) has provided a brief, but adequate review of the available literature. The primary mechanisms of action of ibuprofen and pseudoephedrine are reviewed adequately, and there is no discussion of secondary pharmacology or of safety pharmacology. It is accepted that there is sufficient clinical experience with these compounds and combination, and further revision of the non-clinical pharmacology section is not necessary.

III.3.1 Pharmacokinetics

The pharmacokinetics of the active substances, ibuprofen and pseudoephedrine hydrochloride is adequately discussed in the MAH’s non-clinical overview and are briefly summarised below.

Absorption

14C-labelled ibuprofen was used to study pharmacokinetic parameters following a single oral dose in rats, rabbits and dogs (20, 60 and 8 mg/kg respectively). Ibuprofen was shown to be rapidly absorbed in all three species, with the rate of absorption being fastest in rats and slower in rabbits and dogs with the radiolabel not appearing in the plasma until 45 minutes post dose, compared to after 10 minutes in rats.

In rats, the main site of absorption was determined to be the intestine. Female rats were administered 14C-ibuprofen (20 mg/kg) via oral gavage one hour after ligation of either the pylorus or the small intestine (at the pyloric and ileocaecal junction). At various intervals after dosing (3 to 90 minutes), the radiolabel was quantified in the blood, stomach, stomach contents, intestine and intestinal contents. Absorption was very rapid in the intestine, where the maximal plasma concentration was reached within 3 minutes of dosing, and only 40% of the dose was recovered from the intestine at this time point. In contrast, at 3 minutes post dose, 73% of the dose remained in the stomach. In addition, plasma concentrations were consistently higher in animals with intact intestinal absorption compared to those, where only stomach absorption could occur.

Distribution

In rats, administration of a single oral dose of 14C-labelled ibuprofen (20 mg/kg) showed the presence of the radiolabel in the thyroid 17 hours post dose. Following administration of 20 mg/kg ibuprofen twice
daily for 55 days, there was accumulation of radiolabel in the adrenals, ovaries, fat, thyroid and to a smaller degree, in the skin.

In beagle dogs, \( ^{14}\)C-labelled ibuprofen (8 mg/kg, oral) twice daily for up to 14 days, tissue radioactivity did not exceed that found in plasma.

**Metabolism**
In rabbits dosed with \( ^{14}\)C-labelled ibuprofen (20 mg/kg), the ibuprofen metabolite B was present in plasma in similar amounts to parent ibuprofen, but to a smaller degree in rats. Rat and rabbit plasma also contained metabolites A and C present in smaller amounts. Metabolite D was also observed in rabbits but was not present in rats. Dogs showed no presence of ibuprofen metabolites, with all radioactivity in the plasma considered to be parent ibuprofen.

**Excretion**
The biliary and urinary excretion of ibuprofen and its metabolites were determined in rats after intravenous and per oral administration of 25 and 100 mg/kg of the drug. Within 24 hours 48% of the low i.v. dose and 59% of the high i.v. dose was eliminated via bile as ibuprofen and its metabolites.

Following oral administration 40 to 41% of the dose were recovered in bile, whereas 16 to 32% of the dose were eliminated in urine, resulting in an overall drug recovery of 66 to 79% within 24 hours. Upon infusion of bile containing ibuprofen and its metabolites into the duodenum substantial enterohepatic cycling of the drug occurred in the rat.

**Pharmacokinetic drug interactions**
While ibuprofen is highly plasma protein bound, it is not likely that this binding will displace other drugs at therapeutic concentrations, as ibuprofen would only occupy a small fraction of available sites. Unpublished studies appear to suggest an apparent interaction between ibuprofen acetylsalicylic acid and acetaminophen in rats resulting in a reduction in plasma ibuprofen levels.

**Pharmacokinetics of Pseudoephedrine**
In a study investigating the oral and intravenous pharmacokinetics of pseudoephedrine (0.5 mg/kg) in rats, dogs and monkeys, the oral bioavailability of pseudoephedrine was 38, 58 and 87% in rats, dogs and monkeys respectively. These differences were likely due to due to difference in clearance which was 78, 33 and 15 mL/min/kg respectively. The volume of distribution at steady-state ranged between 3-5 L/kg.

In rats, the half-life \((t_{1/2})\) of pseudoephedrine is short, with values ranging between 30 minutes to 1.5 hours. Values of 1.4 hours and 4.6 hours have been reported in dogs and monkeys respectively.

In rats, clearance occurs via both hepatic and renal systems, but in dogs pseudoephedrine is primarily cleared via the kidneys.

**Overall conclusion on pharmacokinetics**
There are a limited number of publications presented concerning the non-clinical pharmacokinetics of ibuprofen and in particular pseudoephedrine. In addition, most of these publications are fairly old. However, it is accepted that there is sufficient clinical experience with these compounds, and further revision of the non-clinical pharmacokinetics section is not necessary

**III.4 Toxicology**
The toxicological properties of ibuprofen and pseudoephedrine hydrochloride are discussed in detail in the MAH’s non-clinical overview. The summaries of these findings are presented below:
Single dose toxicity
Ibuprofen
The LD$_{50}$ for ibuprofen has been reported to be between 800 mg/kg (oral administration) and 320 mg/kg (intraperitoneal administration) in mice and between 1600 mg/kg (oral administration) and 1300 mg/kg (subcutaneous administration) in rats. In rats, acute signs of toxicity included sedation, prostration, loss of righting reflex and laboured breathing. Regardless of administration route, death occurred within three days as a result of gastric/intestinal ulceration. In another study, ibuprofen LD$_{50}$ values were reported to be 897 mg/kg in mice and 969 mg/kg in rats after oral administration. Similar clinical observations were reported in this study, and gastric ulceration was also observed.

Pseudoephedrine
The reported LD$_{50}$ values for pseudoephedrine range between 105 mg/kg in Beagle dogs to 2206 mg/kg in rats following oral administration. Acute signs of toxicity included increased respiration, salivation, lacrimation, loss of papillary reflex, tremors, convulsions and cardiac arrhythmia. As indicated by the LD$_{50}$, the dog appears more sensitive, potentially related higher sensitivity of this species to compounds that affect the CNS.

Repeat-dose toxicity
Ibuprofen
In rats administered with ibuprofen once daily by oral gavage for four days, 100% of animals presented with stomach and intestinal ulcers after a 200 mg/kg dose. The minimal dose required to cause gastric ulcers was 25 mg/kg and 50 mg/kg for intestinal ulcers. The gastric toxicity of ibuprofen in well-known and is thought to involve the inhibition of constitutively expressed COX-1 within the mucosal epithelium, vascular epithelium, and smooth muscle of the tunica muscularis (responsible for peristalsis). The inhibition of COX-1 can lead to a reduction of endogenous protective mechanisms, decreased mucosal resistance, increased cytokine production, neutrophil adherence and induction of apoptosis.

In a 26-week rat toxicity study in which ibuprofen was administered at doses of 7.5, 20, 60 and 180 mg/kg via oral gavage, the NOAEL was determined to be 60 mg/kg, based on findings of intestinal ulcers in one male and three females in the 180 mg/kg dose group. This finding was also associated with anaemia. Other changes included increased organ weight (liver, kidney, spleen). In a 13-week rat toxicity study in which ibuprofen was administered at doses of 7.5, 20, 60 and 180 mg/kg via oral gavage, a three-week reversibility phase was incorporated. As in the 26-week study, the NOAEL was considered to be 60 mg/kg, based on intestinal ulcers and peritonitis in the 180 mg/kg dose group, with associated anaemia. Increases in organ weights were also observed, but these were demonstrated to be largely reversible.

High doses of ibuprofen have also been shown to cause kidney toxicity. This may be related to the expression of both COX-1 and 2 in the kidney, and their involvement in regulation of fluid balance and blood pressure.

Pseudoephedrine
The National Toxicology Program (NTP) conducted several chronic toxicity studies in different animal models with ephedrine sulfate, a structurally related drug with similar pharmacological properties to pseudoephedrine.

A 14-day repeated-exposure study in rodents showed no deaths attributed to the toxicity of ephedrine sulfate (rats of each sex received diets containing 0-1,500 ppm and mice received diets or drinking water containing 0-5,000 ppm). The most common clinical observations were hyperactivity and excitability,
producing the highest incidence in animals treated at > 1,000 ppm. Reduced weight gain associated with the compound in both sexes was observed in both mice and rats. Reducing body weight gain was also observed in studies of shorter duration in simian and obese mice receiving ephedrine.

This decrease in body weight gain had no effect on survival or increased the incidence of toxic discoveries in these animals at high doses. No serious injury related to the compound at necropsy or histological examinations was observed.

In another 13-week study, rats of each sex were given diets containing 0, 125, 250, 500, 1,000, or 2,000 ppm ephedrine sulfate and mice of each sex were given diets containing 0, 310, 630, 1,250, 2,500, or 5,000 ppm ephedrine sulfate. The major response that occurred during the 13-week studies was compound-associated reduction in weight gain.

The no observed effect level (NOEL) was greater than 250 ppm in rats and mice. Likewise, it was determined that the following clinical signs were related to the compound: coarse hair, hyperexcitability and fights between males. Histopathology scans revealed no compound-related effect.

**Genotoxicity**

**Ibuprofen**

Ibuprofen has been evaluated in the Ames assay in a range of Salmonella typhimurium stains (TA97, TA98, TA100, TA102, TA1535, TA1537 and TA1538) with and without metabolic activation. These tests have confirmed that ibuprofen is not mutagenic when tested at concentrations up to 5000 µg/plate.

No *in vitro* clastogenicity studies of ibuprofen have been reported.

In mice, intraperitoneal injection of 25, 50 and 100 mg/kg ibuprofen showed a weak genotoxic potential at doses ≥50 mg/kg, indicated by increased sister chromatid exchange in bone marrow cells. In human lymphocytes isolated from patients with rheumatoid diseases before and after therapeutic administration of ibuprofen (1200 mg/day) for two weeks, there was no change in sister chromatid exchange rates during the treatment period.

**Pseudoephedrine**

Genotoxicity studies conducted with ephedrine sulfate demonstrated its lack of mutagenic potential in four strains of Salmonella typhimurium (TA100, TA1535, TA97, or TA98) with or without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver 89 activation.

Ephedrine sulfate did not induce sister-chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells.

In another study the ephedra’s mutagenic activity in the Bacillus subtilis rec-assay and the reversion test with S. typhimurium strains TA98 and TA100 (Ames test). No evidence of mutagenic activity was observed. These studies demonstrated the lack of mutagenicity of ephedra and its active ingredient, ephedrine.

This conclusion was confirmed by another research group due to the negative results obtained with ephedra in Ames test (S. typhimurium TA98 and TA100) and in chromosomal aberration and micronucleus assays with mice.

**Ibuprofen and pseudoephedrine**
The mutagenic potential of the ibuprofen-pseudoephedrine combination was assessed in a GLP-compliant Ames test in the *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537 (Study AB04BL-BM.503.BTL). The combination was tested in a fixed ratio of 87% ibuprofen and 13% pseudoephedrine hydrochloride at concentrations up to 5000 µg/plate in the presence or absence of metabolic activation. No significant toxicity was observed at any dose level, and the combination of ibuprofen and pseudoephedrine did not elicit a mutagenic response in this study.

**Conclusion**
A weak genotoxic potential has been reported for ibuprofen in mice, and the genotoxic potential of pseudoephedrine alone has not been determined. However, due to the well-established clinical safety of ibuprofen and the absence of carcinogenic potential (see below), this finding does not raise a cause for concern.

**Carcinogenicity**

**Ibuprofen**
The carcinogenicity of ibuprofen was investigated in mice (50/sex) dosed with 300 mg/kg ibuprofen admixed in the diet for 80 weeks. By week 43, the ibuprofen dose level was reduced to 100 mg/kg, due to the occurrence of mortality as a result of intestinal ulceration and perforation. At the end of the study, there were no treatment-related increases in neoplastic (benign or malignant) lesions in animals receiving 300/100 mg/kg ibuprofen. Non-neoplastic lesions related to ibuprofen were limited to the gastro-intestinal findings.

In rats, ibuprofen (180 /mg/kg admixed in the diet) was administered to male and females (30/sex/dose group) for 104 weeks. As in the mouse study, the dose level was reduced to 60 mg/kg by week 55, due to increased mortality from gastric lesions. At the end of the study, there were no ibuprofen-related increases in neoplastic lesions, and non-neoplastic lesions were related to gastric ulcerations only.

**Pseudoephedrine**
Two-years studies in rats and mice under the auspices of the US National Toxicology Program demonstrated no evidence of carcinogenic potential with ephedrine sulfate at dietary doses up to 10 and 27 mg/kg, respectively (approximately 1/3 and ½ respectively, the maximum recommended daily dose of pseudoephedrine in adults on a mg/m² basis).

Neoplasms that occurred in these studies were not considered to be related to administration of ephedrine sulfate. Two high dose female mice had ovarian granulosa cell tumours, and luteomas were found in one low dose and one high dose female mouse.

Because of the low incidence, these uncommon, benign tumours could not be clearly related to ephedrine sulfate administration. Pseudoephedrine hydrochloride is not considered to be a carcinogen by IARC, NTP or OSHA.

**Reproductive and Development Toxicity**

**Ibuprofen**
The impact of ibuprofen on fertility has been investigated in rats (10 males and 20 females) administered an equivalent dose of 20 mg/kg/day in the diet for 60 days prior to mating. During mating (14 days), females were housed two to a cage with one male, and the animals received a diet without ibuprofen. No noteworthy effects on male and female fertility were observed in this study. Pregnancy was achieved in 15/20 females treated with ibuprofen during the pre-mating period, compared to 16/18 females in the control group. Prior to parturition, two females in the ibuprofen group died or were euthanised due to vaginal haemorrhage. One female had gastric ulcers and anaemia, and the other had lung congestion and...
a clot in one uterine horn. At parturition, the litter size was similar between the ibuprofen and control groups (average 7.9 live young per litter compared to 7.3 live young per litter in controls).

The potential teratogenicity of ibuprofen was investigated in mated female rats dosed with 7.5, 20, 60 and 180 mg/kg/day by oral gavage from GD1 to GD20. All animals were euthanised on GD21 for examination of uterine content. Maternal toxicity was observed in animals receiving ibuprofen at ≥20 mg/kg, evidenced by dose-dependent findings of gastrointestinal lesions. However, only females in the 180 mg/kg dose group showed concurrent reduced body weight gain, and there was no impact on fetal weight and litter size. Observed variations in number of fetuses (alive or dead) were not related to dose level, and there was no dose-dependent effect on the number of abnormal fetuses.

In another study, in which ibuprofen was administered to rats throughout the pregnancy (7.5 and 20 mg/kg), and the delivered litters allowed to grow until weaning, there were no effects on weaning viability, weight and malformations.

More recent studies in rats have employed more frequent dosing of ibuprofen to compensate for the short half-life. Pregnant Wistar rats given total daily doses of 25.5, 255 and 600 mg/kg/day (administered in three daily doses) from GD8-21 showed signs of maternal toxicity at doses ≥255 mg/kg. At these dose levels, there was also an increase in external (≥255 mg/kg) and skeletal (600 mg/kg) fetal variations, although this may have been attributed to maternal toxicity. In this study, 255 mg/kg was considered to be the NOAEL for developmental toxicity.

In rats receiving ibuprofen (three times daily at 0.3, 3 and 200 mg/kg) from GD8-21, there was a decrease in fetal mineralization. However, this effect was only observed at maternally toxic doses.

In rabbits, ibuprofen was administered orally (7.5, 20 and 60 mg/kg/day) from GD0 to GD29 of pregnancy, and animals were euthanised on GD30 for analysis of uterine contents. Some changes were noted in maternal body weight at doses ≥20 mg/kg, and two females in the 60 mg/kg dose group delivered early on GD26 and 28 (litters were normal). In addition, females in the 60 mg/kg dose group had stomach ulcers, and some also showed evidence of focal hepatitis, perhaps due to infection secondary to the gastric lesions.

There was a slight reduction in the number of live fetuses per litter in the 60 mg/kg dose group compared to control, but average fetal weight was normal across the dose groups. In this study, there was no evidence of fetal malformations linked to the treatment with ibuprofen.

Only one study concerning the effects of ibuprofen on early postnatal development has been described. This study was not of a traditional pre-and postnatal development study design, and only provided information relating to the effects of ibuprofen on kidney development in preterm baboons. Prematurely delivered baboons (GD 125 compared to term as GD185), received five intravenous doses of ibuprofen (10 mg/kg 24 hours post-delivery and 5 mg/kg at 48, 72, 96 and 120 hours post-delivery). Ibuprofen did not affect glomerular generation number or the percentage of abnormal glomeruli but did lead to a reduction in the nephrogenic zone.

**Pseudoephedrine**

In animal studies, pseudoephedrine reduced average weight, length, and rate of skeletal ossification in animal fetus.

The developmental toxicity of pseudoephedrine was evaluated with the FETAX (Frog Embryo Teratogenesis Assay: Xenopus) by exposing late Xenopus laevis blastulae to pseudoephedrine for 96 h. At concentrations >200 mg/l, pseudoephedrine produced miscoiling of the gut and skeletal kinking.
Exposure to concentrations >250 mg/ml induced pericardial and craniofacial edema, as well as microphthalmia. Abnormal development of the mouth and blistering of the dorsal fin were noted at concentrations exceeding 280 mg/l. The authors concluded that, according to pseudoephedrine’s score of 1.9 in the Teratogenic Index, this compound has a moderate teratogenic potential.

Pregnant Wistar rats received 240 mg/kg bw of pseudoephedrine HCl on days 6-15 of gestation. At least effects on dams’ body weight and food consumption and fetal weight and ossification were investigated. An influence of pseudoephedrine HCl on the dams as well as on the fetuses was reported. It was concluded that, based on the available data, a developmental toxicity effect of the test substance in rats cannot be ruled out, but may only occur at maternal toxic doses.

**Conclusion**

While the presented fertility study did not indicate an effect of ibuprofen on fertility, it should be noted that there is evidence suggesting that drugs that inhibit COX and prostaglandin synthesis may cause impairment of female fertility by affecting ovulation. This is covered in sections 4.6 and 5.3 of the SmPC.

Although some fetal variations have been observed at maternally toxic doses, there is no non-clinical evidence for ibuprofen teratogenicity. However, ibuprofen is contraindicated during the third trimester of pregnancy, due to a risk of premature closure of the fetal ductus arteriosus (with possible persistent pulmonary hypertension), delayed labour and increased bleeding tendency. These effects are related to the inhibitory action of ibuprofen on prostaglandin synthesis and are reflected in sections 4.3 and 4.6 of the SmPC.

The effect of ibuprofen and pseudoephedrine on prenatal and postnatal development has not been adequately assessed from a non-clinical perspective. However, it is accepted that there is sufficient clinical experience with both substances, and further revision of the non-clinical sections is not necessary.

**Other Toxicity Studies**

**Toxicity of ibuprofen-pseudoephedrine HCl combination**

This section contains extracts from public assessment reports published from competent authorities which are not valid sources of information for a 10a application. Evidence of safety is therefore deficient from the non-clinical perspective. The lack of admissible data however can be justified as there is sufficient evidence of clinical use of this combination (EMEA/CHMP/SWP/258498/2005). This has been conclusively proven in the clinical part and further non-clinical data is therefore unnecessary.

**Impurities and Excipients**

A discussion of impurities and excipients has been included in the non-clinical overview, and in addition the relevant sections of this application have also been reviewed.

**Drug Substances**

Ibuprofen is manufactured in accordance with an EDQM Certificate of Suitability. Impurities in the drug substance and drug product are controlled as per the current version of the European Pharmacopoeia.

Pseudoephedrine hydrochloride is manufactured in accordance with an EDQM Certificate of Suitability. Impurities in the drug substance and drug product are controlled as per the current version of the European Pharmacopoeia.

**Drug Product**
All excipients used, are described in the European Pharmacopoeia, except thaumatin (E-957) and orange flavour that meet the manufacturer’s in-house specifications. Orange flavour contains E-320 butylated hydroxyanisole (0.08%), E-307 alpha tocopherol (0.04%), flavouring substances and flavouring preparations. The excipients are acceptable and require no further toxicological qualification.

Conclusion
The MAH provides a short discussion of impurities and excipients in the non-clinical overview. There are no toxicological concerns with impurities in the drug substances and drug product or use of excipients.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Ibuprofen and Pseudoephedrine hydrochloride Formalider oral suspension is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint. The MAH has discussed the toxicity of ibuprofen and pseudoephedrine hydrochloride in some detail. In general, the non-clinical toxicity profile of ibuprofen has been adequately studied, although most studies are not recent. Several aspects of pseudoephedrine hydrochloride non-clinical toxicology has not been adequately characterised in the literature, including repeat dose toxicity, genotoxicity, carcinogenicity, reproductive development. However, based on the extensive clinical experience with pseudoephedrine hydrochloride, the limited amount of non-clinical data is not considered a cause for concern.

Combination studies and embryo-fetal development studies did not reveal any new toxicity when ibuprofen and pseudoephedrine hydrochloride were evaluated in combination. However, this section contains extracts from public assessment reports published from competent authorities which are not valid sources of information for a well-established use application. Evidence of safety is therefore deficient from the non-clinical perspective. The lack of admissible data however can be justified as there is sufficient evidence of clinical use of this combination (EMEA/CHMP/SWP/258498/2005). This has been conclusively proven in the clinical part and thus further non-clinical data is deemed unnecessary.

While there is no clear non-clinical evidence for ibuprofen-related reproductive toxicity, due to ibuprofen’s effect on prostaglandin synthesis (as is the case with any NSAID), its use is contraindicated in pregnancy, and it is not recommended in women trying to conceive (see section 4.6 of the SmPC). The non-clinical overview does not include any non-clinical information relating to the potential excretion of ibuprofen and pseudoephedrine into the breast milk. However, the SmPC confirms that a small proportion of both substances may be excreted into the breast milk.

A discussion of impurity profiles in the drug substance and drug product has been included in the Non-Clinical Overview. Similarly, drug product excipients have been discussed in the non-clinical overview. Following additional review of the quality aspects of this application, there are no toxicological concerns with impurities and excipients in the drug substance and drug product.

IV CLINICAL ASPECTS
IV.1 Introduction
Ibuprofen and pseudoephedrine hydrochloride are well-established active substances, with recognised efficacy and acceptable safety, and the active substances have been licenced both separately and in combination in the European Union for many years. The details of their pharmacology are documented in various publicly accessible sources and a comprehensive review of the published literature has been
provided by the MAH, citing the well-established clinical pharmacology, efficacy and safety of ibuprofen and pseudoephedrine hydrochloride. The clinical overview has been written by an appropriately qualified person and is considered acceptable.

**IV.2 Pharmacokinetics**

**Introduction and overview**

**Ibuprofen:**
Ibuprofen is rapidly absorbed from the gastrointestinal tract, and its plasma concentrations reach a maximum peak level about 2 hours after administration. Elimination half-life is approximately 2 hours. Ibuprofen is metabolised in the liver into two major inactive metabolites and these together with unchanged ibuprofen are excreted by the kidney either as such or as conjugates. Excretion by the kidney is both rapid and complete. Ibuprofen is extensively bound to plasma proteins.

**Pseudoephedrine:**
Pseudoephedrine is absorbed in the gastrointestinal tract and is largely excreted in the urine unchanged, together with small amounts of a hepatic metabolite. It has an elimination half-life of several hours, which may be reduced by acidifying the urine.

To further support this application, the MAH has performed a bioequivalence study to show that the relative bioavailability of the test product; ibuprofen 200 mg/ pseudoephedrine hydrochloride 30 mg (ibuprofen 20mg/ml and pseudoephedrine hydrochloride 3mg/ml) is comparable to administration of these active ingredients in the already approved products Junifen 20 mg/ml Oral Suspension Orange Flavour (ibuprofen) [Reckitt Benckiser Healthcare S.A. Spain] and Sudafed Decongestant Liquid (McNeil Products Limited) which contains 30 mg pseudoephedrine hydrochloride given concomitantly.

**STUDY:**
Randomised crossover bioequivalence study to evaluate the bioavailability between 200mg/30 mg of ibuprofen/pseudoephedrine hydrochloride (20mg/ml / 3mg/ml oral suspension) versus already approved products; 200 mg of Junifen 20 mg/ml Oral Suspension Orange Flavour (ibuprofen) plus 30 mg of Sudafed Decongestant liquid (pseudoephedrine hydrochloride), after a single dose administration to healthy fasted volunteers.

Following an overnight fast of at least 10 hours, subjects administered a single oral dose of the combination test product (200mg ibuprofen/ 30 mg pseudoephedrine) or already approved separate reference products Ibuprofen 200 mg (Junifen) and pseudoephedrine hydrochloride 30 mg (Sudafed decongestant liquid) with 240 ml of water. Blood samples were collected for plasma levels before dosing and up to and including 24 hours after the drug administration. The washout period between treatment phases was 3 days.

The study design measured determination of the plasma concentrations of pseudoephedrine and both enantiomers of ibuprofen.

The main pharmacokinetic results are presented below:
Conclusion

The 90% confidence intervals for R-ibuprofen, S-ibuprofen and pseudoephedrine lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the MAH’s combination product Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension is bioequivalent to the already approved similar products Junifen 20 mg/ml Oral Suspension Orange Flavour Reckitt Benckiser Healthcare S.A., Spain) and Sudafed Decongestant liquid (McNeil Products Limited, UK) when administered concomitantly.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for this bibliographic application. The pharmacodynamic properties of pyridoxine hydrochloride are discussed in detail in the MAH’s clinical overview. The summaries of these findings are presented below.

Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension is a medicine consisting of a combination of two active substances: ibuprofen and pseudoephedrine. Pseudoephedrine is a sympathomimetic agent with direct and indirect effects on adrenergic receptors. It has alpha and beta stimulant adrenergic stimulant activity and some stimulant effect on the central nervous system. The sympathomimetic effect of pseudoephedrine produces vasoconstriction which relieves nasal congestion. Ibuprofen is an anti-inflammatory analgesic and antipyretic drug belonging to the group of non-steroidal anti-inflammatory drugs. In humans it has been shown to be effective in reducing the symptoms (pain, fever and swelling) associated with inflammation and influenza. The therapeutic effects of the drug are the result of an inhibitory activity on the prostaglandin synthesis.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81mg), a decreased effect of acetyl salicyclic acid (ASA) on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.
IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type. The MAH discussed the evidence of safety and efficacy of the combined formulation of ibuprofen and pseudoephedrine in the EU for at least 10 years and a summary based upon the literature review is presented below:

**Efficacy of the Ibuprofen/pseudoephedrine combination**

**Nasal congestion and URI symptoms**

The following studies were discussed in literature publications:

- A double-blind, randomised, single-dose study with subjects with nasal congestion associated with upper respiratory tract infection.

  Following a single dose of 200mg/30mg (n=100), 400mg/60mg, or placebo (PBO), subjects rated at regular intervals over 4 hours the degree of nasal congestion on a 100-mm visual analog scale and nasal congestion relief on a 6-category scale. At all-time points as well as overall, 400mg/60mg provided significantly (p<0.05) greater relief and reduction of nasal congestion than 200mg/30mg and PBO; 200/30 was significantly different from placebo at most timepoints as well as overall.

- A double-blind, multiple-dose, actual-use trial in subjects with URI to assess the efficacy of the combination of ibuprofen 200 mg with pseudoephedrine 30 mg in subjects with symptoms requiring the use of both a decongestant and an analgesic/antipyretic. Subjects were randomly assigned to receive ibuprofen/pseudoephedrine acetaminophen 500 mg + pseudoephedrine 30 mg, or placebo (PBO) and instructed to take 1-2 capsules q4-6h up to 6 capsules per day, as needed, for up to 10 days. Each day of dosing, subjects assessed treatment efficacy on a 4-category Global Evaluation (0 = not effective to 3 = very effective). For days 1-6 of dosing, the Global Evaluation for ibuprofen + pseudoephedrine and acetaminophen + pseudoephedrine was significantly better than PBO (P<0.05). These results show the efficacy of ibuprofen + pseudoephedrine and acetaminophen + pseudoephedrine in treating symptoms of URI.

- A randomised, double-blind, placebo-controlled study in patients with experimental rhinovirus colds. Patients included in the study were randomly assigned to receive two identically appearing capsules containing pseudoephedrine HCl 60 mg and ibuprofen 200 mg, pseudoephedrine HCl 60 mg and placebo, or both placebos four times daily for 41/2 days beginning 30 hours after intranasal rhinovirus inoculation.

  The frequency and severity of illness were determined by twice daily recording of the volunteers' symptoms: nasal (discharge, obstruction, sneezing), throat (sore throat, hoarseness, cough) and systemic (headache, chills, feverishness, malaise) on a four-point scale (0-3, absent to severe). The higher of the two daily ratings was used as the score for that day. Objective measures of illness severity included morning and evening oral temperatures; daily collection of nasal tissues for tissue counts and determination of nasal secretion weights (post-challenge days two-six) by previously described methods; and nasal patency measurements by anterior rhinometry prior to and 45 and 90 minutes after administration of the drug doses. Subjects completed the study (23 received pseudoephedrine alone, subjects received pseudoephedrine plus ibuprofen, and 10 received placebo). Illness severity was reduced by both pseudoephedrine alone and in combination with ibuprofen. Total symptom scores were significantly reduced by pseudoephedrine plus ibuprofen, and a similar trend was found with pseudoephedrine alone. Nasal symptom scores tended to be reduced in recipients of pseudoephedrine plus ibuprofen compared with pseudoephedrine alone, but other subjective and objective measures of efficacy did not detect significant differences between the active treatment groups. Rhinorrhoea, as reflected in nasal mucus weights, was significantly less in either treatment group compared with
placebo. Nasal patency tended to be greater among the recipients of pseudoephedrine plus ibuprofen compared with placebo or with pseudoephedrine alone.

Conclusion
The results of the above studies showed that the combination of pseudoephedrine with either ibuprofen or acetaminophen were statistically significant superior to placebo.

Efficacy of Ibuprofen

Fever
A number of controlled studies have been presented that demonstrate the drug’s antipyretic properties. Two recent reviews compare the efficacy and safety of ibuprofen to that of paracetamol in the treatment of pain and fever. From the evaluation of randomized clinical trial studies that directly compared ibuprofen to paracetamol, it was confirmed the analgesic and antipyretic efficacy and safety of ibuprofen in children and adults. Moreover, it was demonstrated that ibuprofen is as or more efficacious than paracetamol and equally safe.

In children, it is noteworthy that ibuprofen showed similar efficacy but with a faster onset of action than paracetamol.

A review of studies that compare the effectiveness of ibuprofen and paracetamol in reducing fever was conducted. It emerged that both drugs are more effective than placebo in reducing fever.

In some randomised single-blind clinical trials it has been also compared the antipyretic effectiveness of ibuprofen in children to paracetamol or dipyrone efficacy. Data from these studies show that oral ibuprofen (7mg/kg-10 mg/kg) has a greater or similar efficacy than paracetamol (15mg/kg) or dipyrone (15 mg/kg), respectively. In addition, ibuprofen (7.5 mg/kg) has shown to be more effective than aspirin (10 mg/kg) in reducing fever for a period of 6 hours in children between 6 and 24 months of age.

Regarding the dose–efficacy relationship of ibuprofen used as antipyretic in children between 3 months and 12 years of age, the different studies point out that within the range of 5 to 10 mg/kg and administered every 6 to 8h (20-30 mg/kg/day) ibuprofen shows a good antipyretic efficacy while a 0.625 mg/kg dose proves ineffective to maintain the decrease in temperature during the 3 hours that follow the administration of the initial dose, requiring rescue medication, ibuprofen 2.5 mg/kg, the 68% of patients.

The antipyretic effect of a single dose of the specific COX-2 inhibitor rofecoxib (25 mg) was compared with that of ibuprofen (400 mg) in a randomized, double blind study, conducted in 94 adults with fever of viral origin. Both antipyretics produced a comparable decrease of temperature 4 hours after administration; however, the antipyretic effect appeared earlier with ibuprofen than with rofecoxib.

The studies presented above compared the antipyretic properties of ibuprofen and acetaminophen in adults and children and were found to be comparable.

The MAH has provided enough evidence to support the use of ibuprofen as antipyretic. Furthermore, as already stated by the applicant, Ibuprofen is listed in the WHO (world health organisation) list of essential medicines for adults and children.

Pain in cold and influenza
A blinded, multicentre study in general practice of up to 7 days of aspirin, paracetamol (both up to 3g daily) or ibuprofen (up to 1.2g daily), administered for common painful conditions, using patient generated data with physician assistance.
The main indications were musculoskeletal or back pain (48%), sore throat, the common cold and flu (31%) (please see table 15). The overall tolerability of ibuprofen in this large-scale study was equivalent to that of paracetamol and better than that of aspirin. These findings could lead to a reassessment of the use of first-line analgesics for the short-term management of painful conditions in general practice, recommending ibuprofen first, because of the poor tolerability of aspirin and the potential risks of paracetamol overdose. In relation to the effect of treatment, on global evaluation, 74.2% of patients on ibuprofen rated the treatment as excellent or good, a significantly higher rating than for paracetamol (69.2%) or aspirin (68.6%) [both p < 0.001]. The study data can be evaluated as supportive for the efficacy and general accepted use of ibuprofen for treatment of cold and influenza.

Baseline characteristics are presented below:

<table>
<thead>
<tr>
<th>Indication</th>
<th>43.5 (14.7)</th>
<th>43.3 (14.7)</th>
<th>43.6 (14.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal pain</td>
<td>925 (32.0%)</td>
<td>954 (33.3%)</td>
<td>907 (31.6%)</td>
</tr>
<tr>
<td>Cold/flu</td>
<td>586 (20.3%)</td>
<td>571 (19.9%)</td>
<td>548 (19.1%)</td>
</tr>
<tr>
<td>Backache</td>
<td>461 (16.0%)</td>
<td>431 (15.0%)</td>
<td>476 (16.6%)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>317 (11.0%)</td>
<td>352 (11.6%)</td>
<td>341 (11.9%)</td>
</tr>
<tr>
<td>Headache</td>
<td>304 (10.5%)</td>
<td>297 (10.4%)</td>
<td>291 (10.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>126 (4.4%)</td>
<td>105 (3.7%)</td>
<td>123 (4.3%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>112 (3.9%)</td>
<td>116 (4.0%)</td>
<td>113 (3.9%)</td>
</tr>
<tr>
<td>Pain of menstrual cramps</td>
<td>55 (1.9%)</td>
<td>59 (2.1%)</td>
<td>65 (2.3%)</td>
</tr>
</tbody>
</table>

A single dose of ibuprofen, aspirin, and paracetamol for the treatment of headache were evaluated. The study included patients aged 18-60 who sought the advice of the pharmacist for headache. The four treatment options comprised single doses of 400 mg ibuprofen, 650 mg or 1000 mg aspirin, and 1000 mg paracetamol. Immediately before treatment, the patients were asked to score their headache on a nine-point scale and were then asked to re-assess headache pain 15 minutes, 30 minutes, one, two and three hours after treatment. Overall, ibuprofen provided significantly more pain relief than either aspirin 650 mg or paracetamol. The relief of common cold pain-related symptoms has also been evaluated for ibuprofen and paracetamol. In a double-blind, single-dose, parallel group clinical study, using sore throat as an indicator, patients with tonsillopharyngitis were asked to compare pain relief with paracetamol and ibuprofen. Patients were asked to assess pain relief every hour for six hours after receiving placebo, paracetamol, or ibuprofen. Between 3-6 hours after receiving a single dose, ibuprofen provided significantly greater pain relief and pain intensity than paracetamol. The review concluded that ibuprofen offers significant relief from sore throat and headache, two of the main symptoms associated with the common cold.

Two recent reviews confirm this conclusion and support the efficacy of ibuprofen in the relief of symptoms of cold and flu. Even, states that in terms of benefits, ibuprofen at OTC recommended doses has been proven to have either comparable or in many cases superior therapeutic effects to those of other NSAIDs or analgesics in the treatment of a wide variety of painful and associated inflammatory conditions, including upper respiratory tract infections, colds and influenza.

Different types of pain, including common cold symptoms, were assessed in the studies presented above and the efficacy of ibuprofen (1.2 g daily) was compared to paracetamol and aspirin. Studies assessed the efficacy of paracetamol, ibuprofen (400mg) and aspirin on headache and sore throat. Reviews and data support the use of Ibuprofen at the proposed dose (200-400mg) as analgesic for headache and sore throat which are common cold symptoms.
**Pseudoephedrine**

A study was conducted in order to determine the efficacy of pseudoephedrine in the treatment of nasal symptoms associated with the common cold or flu. It was a multicentre, open clinical trial, administering one pseudoephedrine capsule every 12 hours during 4 consecutive days in order to relieve the nasal symptomatology associated to flu and/or common cold processes. A number of patients were suitable for analysis of efficacy. According to the results, these authors concluded that pseudoephedrine was a drug substance for the symptomatic control of nasal affection present in flu and/or common cold symptoms. Therefore, the volume of patients, data handled, methodological rigour of the study and data displayed are highly significant.

To note, no placebo or comparator was used in this study; therefore, this cannot be deemed supportive for the scope of this application.

A review discussed the double-blind, placebo-controlled trial to assess the efficacy of pseudoephedrine in the relief of nasal congestion associated with the common cold. Previously healthy individuals with a common cold for 5 or fewer days prior to the start of the study were included. All these presented moderate to severe nasal congestion. One 60 mg capsule of pseudoephedrine or placebo were administered, showing a significant improvement in the patients that received the drug substance at 60, 90, 120 and 150 minutes. With regard to the methodology used by these authors, the total nasal minimum cross-section area and the nasal volume were measured via acoustic rhinometry, showing a significant increase compared with placebo (p = 0.018 and p = 0.003, respectively) after administration of the dose. No significant changes were shown in the nasal area measured by posterior rhinomanometry. According to these findings, the study authors concluded that, in the acute common cold, a single dose of 60 mg of pseudoephedrine caused a significant increase in the dimensions of the nasal capacity compared with placebo, which was associated to a reduction of congestive symptomatology.

A review discussed a group of patients affected by nasal congestion associated to the common cold received 2 doses of medication separated by a 4-hour interval: pseudoephedrine 60 mg and placebo. The unilateral nasal flow was measured during a 7-hour period to register the spontaneous changes in said flow in association with the nasal cycle. Maximum and minimum flows were defined as the highest and most reduced values detected during the registration period of 7 hours in each nasal pass. There were no significant differences with regard to the maximum flow between the 2 groups, but these appeared with regard to the minimum flow (p < 0.05). These findings highlighted that although pseudoephedrine does not act on the flows in the decongestive phase of the nasal cycle, it is an effective agent in the congestive phase, improving the air flow through the nasal cavities in situations that said phenomenon occurs, such as during the common cold.

A published review discussed the efficacy of oral administration of pseudoephedrine in patients with chronic non-suppurative rhinitis under double-blind conditions. Intranasal administration of ephedrine acted as positive control. The results obtained showed that a single oral dose of pseudoephedrine of 60 mg gave significant nasal decongestant effects. This determination was carried out via modified passive anterior rhinomanometry. Said effects were detected at 30 minutes and were maintained during at least 4 hours. The mean nasal decongestant response was 57.2%, associated to a plasmatic concentration peak of pseudoephedrine of 274 ng/ml. In addition, the maximum oral response to pseudoephedrine was equivalent to the response induced by the nasal application of ephedrine spray. According to the authors of the article, these results suggested that pseudoephedrine administered orally was an effective nasal decongestant agent.
Another two studies showed the efficacy of pseudoephedrine in nasal congestion. However, the strength used in these studies is higher (120mg and 240mg) than the proposed posology (30-60mg); therefore, these studies are not assessed for the scope of this application.

Three supportive studies have been discussed above. In these studies, 60 mg of pseudoephedrine was compared to placebo or with intranasal ephedrine. In all studies, pseudoephedrine showed significant nasal decongestant effect when compared with placebo and comparable effect with intranasal ephedrine. The 60 mg dose used in these studies is in accordance with the proposed 30-60mg dose of pseudoephedrine recommended in the proposed SmPC.

Based on these results, the indication was changed to “nasal congestion” instead of runny nose.

**Dose justification**

**Ibuprofen**

A systematic review and meta-analysis of clinical trials assessed the safety and efficacy of doses of 200mg or 400mg of ibuprofen in the treatment of acute migraine in adults.

Another review discussed the epidemiologic data which supported the use of 400 mg of ibuprofen first when choosing an NSAIDs.

Reviews reported that there is a clear relationship between single doses of ibuprofen over the range 50-400 mg and the peak analgesic effect and the duration of analgesia. Ibuprofen 400 mg has been shown to be as effective as ASA doses of 600 or 900 mg/d in models of moderate pain but superior to ASA or paracetamol in more sensitive models.

A publication discussed “For relief of mild to moderate pain, the usual adult oral dosage of ibuprofen is 400 mg every 4-6 hours as necessary. Alternatively, for self-medication of mild to moderate pain, the usual initial adult dosage is 200 mg every 4-6 hours; dosage may be increased to 400 mg every 4-6 hours if pain does not respond to the lower dosage but should not exceed 1.2 g daily unless directed by a clinician. Moreover, for self-medication of fever, the usual initial adult dosage of ibuprofen is 200 mg every 4-6 hours; dosage may be increased to 400 mg every 4-6 hours if fever is not adequately reduced at the lower dosage”.

**Pseudoephedrine**

A published review discussed the posology of pseudoephedrine as outlined below:

“For nasal congestion and other respiratory conditions, the usual dosage of pseudoephedrine hydrochloride for adults and children 12 years of age or older is 60 mg every 4-6 hours with a maximum of 240 mg daily”.

In summary the bibliographic evidence supports the proposed posology of 200-400mg of ibuprofen and 30-60mg of pseudoephedrine (equivalent of 10-20ml).

The MAH has provided a suitable justification to bridge their product, Ibuprofen and Pseudoephedrine Farmalider oral suspension, to the bibliographic data and is summarised as follows:

The link which allows to bridge Ibuprofen/pseudoephedrine hydrochloride 100mg/5mg per 5ml oral suspension to the bibliographic evidence provided is the bioequivalence study performed which demonstrated bioequivalence between such combination and the reference single constituents, Junifen 20 mg/ml oral suspension and Sudafed Decongestant Liquid (30 mg/5ml).
This bioequivalence study was performed according to the current European guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) and compared the pharmacokinetic properties of a single dose of 200-30 mg of Ibuprofen/pseudoephedrine hydrochloride 100mg/5mg per 5ml oral suspension and the reference products, 200 mg of Junifen 20 mg/ml oral suspension plus 30 mg of Sudafed decongestant liquid. Bioequivalence was demonstrated for AUC0-t and Cmax since the 90% confidence interval for the corresponding mean ratios (test over reference) of both R-Ibuprofen, S-Ibuprofen and pseudoephedrine were completely contained in the predefined bioequivalence acceptance range of 80.00-125.00. Therefore, the extend and the rate of the absorption of the active substances were equivalent between the fixed combination medicinal product and the authorised active substances taken simultaneously, as it is usual in medical practice for the relief of symptoms of the common cold.

The efficacy and safety of these reference products are widely demonstrated as they have an extensive clinical experience in numerous European countries. Thus, Junifen 20 mg/ml oral suspension which belongs to the same global marketing authorisation as Nurofen 20 mg/ml oral suspension by Reckitt Benckiser Healthcare, has been marketed in Spain since April 1999 and Sudafed Decongestant Liquid has been marketed by McNeil Products Ltd. in UK since March 1997 and in Ireland since 1978. The MAH specified that according to Article 10a of Directive 2001/83/EC, as amended, which requires that detailed references to published scientific literature are presented to show that the constituents of the proposed medicinal product have a well-established medicinal use, with recognised efficacy and an acceptable level of safety, the proposed combination, Ibuprofen/pseudoephedrine hydrochloride 100mg/5mg per 5ml oral suspension, is a medicine with “well-established use”. This means that the medicinal use of the active substances of this formulation, both individually and in combination, have been well-established use in the European Union /EU) for at least 10 years.

The active substances of the combination subject of this application, ibuprofen and pseudoephedrine hydrochloride, have been proved to be efficacious and safe for the indications claimed for Ibuprofen/pseudoephedrine hydrochloride 100mg/5mg per 5ml oral suspension both by the bibliographic evidence and by the extensive clinical experience which has demonstrated the therapeutic value of these compounds.

Regarding the bibliographic evidence for the active substances individually, the bibliography included with this application confirms that ibuprofen has a proven efficacy and safety for the indications fever and pain in cold and flu, and specifically several studies have been included in this for ibuprofen in the form of oral suspension moreover some of these studies were performed with the reference medicinal product, Junifen 20 mg/ml oral suspension.

Additionally, the applicant referred to the public assessment report of an Ibuprofen 100mg/5ml Oral Suspension in which several clinical studies in children and adults were assessed such as which allowed to conclude that ibuprofen is a well-known substance and its use in the relief of mild to moderate pain (such as sore throat, teething pain, toothache, earache, headache, minor aches and sprains), in the relief of the symptoms of colds and flu and the reduction of fever is well-established. With respect to Pseudoephedrine, the clinical studies also included with this application demonstrated its efficacy and safety as nasal decongestant in the common cold and flu. Furthermore, the use of ibuprofen and pseudoephedrine hydrochloride in combination for the effective relief of symptoms of the common cold is well-established in the medical practice and it is widely documented in the scientific literature, as discussed previously during this procedure. Additionally, the doses proposed for Ibuprofen/pseudoephedrine hydrochloride 100mg/5mg per 5ml oral suspension have been proven to be efficacious and safe in the indications claimed, by the bibliographic evidence (also included for the registration dossier and updated during this procedure), and by the post-marketing experience of other similar combinations marketed in different European countries, with the same strengths.
Moreover, the MAH referred to other combinations of ibuprofen/pseudoephedrine already authorised in UK, under the same legal basis of “well-established use” as requested in our application, by DCP and national procedures also commented during this procedure. These applications, similarly to our application, were supported by bibliography evidence and by a bioequivalence study in order to show that the combination of the active ingredients (ibuprofen/pseudoephedrine) in a single product was comparable to administration of these active ingredients in separate products. The results of the bioequivalence studies demonstrated bioequivalence and it was considered enough to bridge such combinations to the available bibliographic data on ibuprofen and pseudoephedrine hydrochloride. It has to be highlighted that these combinations present the same strength, pharmaceutical form and indications as for the ibuprofen/pseudoephedrine combination subject of this application.

Additionally, as supportive information, the guideline on the investigation of bioequivalence specifically for Fixed combination dosage forms states that: “Bioequivalence requirements are covered in the “Guideline on Clinical Development of Fixed Combination Medicinal Products”. This guideline for fixed combinations, established for fixed combinations intended to be a substitution therapy in patients adequately controlled with two or more active substances used in combination, such as Ibuprofen/pseudoephedrine hydrochloride 100mg/5mg per 5ml oral suspension, that the demonstration of bioequivalence between the fixed combination medicinal product and the authorised active substances taken simultaneously is required.

Finally, the MAH highlighted that all the excipients used in the ibuprofen/pseudoephedrine combination are well-established and widely-used pharmaceutical excipients and they are not expected to affect the absorption of the drug substances, except maltitol which could affect to the bioavailability, but that according to the results of BE study performed, it had no any effect on the absorption of the active substances since Junifen also contains maltitol but Sudafed does not contain this excipient and the BE was demonstrated for both active substances, ibuprofen (S-ibuprofen and R-ibuprofen) and pseudoephedrine.

In conclusion, taking into account all above, the bioequivalence study conducted by Farmalider is the link between Ibuprofen/pseudoephedrine hydrochloride 100mg/5mg per 5ml oral suspension and the bibliographic evidence provided for Ibuprofen and pseudoephedrine as well as ibuprofen/pseudoephedrine in combination, all the evidence provided is considered representative enough and sufficiently supports the safety and efficacy of Ibuprofen/pseudoephedrine hydrochloride 100mg/5mg per 5ml oral suspension and therefore the present application meets all the requirements for a bibliographic application.

**IV.5 Clinical safety**

No new safety data were submitted, and none are required for this bibliographic application. The safety of ibuprofen and pseudoephedrine hydrochloride is adequately reviewed in the clinical overview. The clinical safety properties of the single active and combination of the actives are discussed in detail in the MAH’s non-clinical overview. The summaries of these findings are presented below.

A study comparing the bioavailability of single doses of Ibuprofen 200mg and pseudoephedrine 30 mg administered alone or in combination as an oral suspension was presented in literature review. The adverse events produced by the ibuprofen/pseudoephedrine hydrochloride combination or each active substance alone were recorded. A total of 14 treatment-emergent adverse events were reported by a number of subjects (of which a number were for the test formulation, for ibuprofen alone and for pseudoephedrine alone). All adverse events were mild and resolved spontaneously.
Two events were considered as possibly related to the test medication. One subject reported forearm itching which was considered definitely related; the event was also reported with pseudoephedrine alone and was also considered possibly related to the study drug. Another subject reported heart burn which was considered as possibly related to the study medication. In addition, itching and generalized body ache were reported as possibly related to ibuprofen alone. There were no clinically relevant changes in vital signs, ECGs or laboratory findings.

A pharmacokinetic study noted two adverse events. One case of diarrhoea and one case of somnolence was reported.

Another review detailed that pseudoephedrine plus ibuprofen were generally well tolerated and no subjects withdrew from the study due to adverse drug effects. Symptoms potentially referable to increased sympathomimetic activity were reported by several subjects receiving pseudoephedrine such as: light-headedness, difficulty sleeping, lethargy or indigestion. There were no adverse effects (i.e., gastric upset) directly attributable to ibuprofen.

The incidences of somnolence and dizziness as discussed in a review were significantly higher in the ibuprofen/pseudoephedrine/chlorpheniramine 2-caplet group compared with the placebo and the other 2 active treatment groups. Dry mouth occurred with a statistically significantly higher incidence in all active treatment groups compared with the placebo group but not with each other. Insomnia also occurred with a statistically significantly greater incidence in the ibuprofen/pseudoephedrine/chlorpheniramine 2-caplet group compared with the placebo group and a numerically greater incidence compared with the other active treatment groups.

**POST MARKETING EXPERIENCE**

**Ibuprofen**

The available data of action taken for safety reasons since ibuprofen was marketed are as follows:

- Cardiovascular events and potentially life-threatening, gastrointestinal bleeding

In July 2005, based on a review of available data from long-term placebo- and active controlled clinical NSAID trials, the FDA concluded that an increased risk of serious adverse cardiovascular events may be a class effect for all NSAIDs, COX-2-selective and nonselective alike (excluding aspirin). In 2006, the Agency’s Committee for Medicinal Products for Human Use (CHMP) concluded that the overall benefit-risk balance remained positive, but the possibility of a small increased risk of thrombotic events such as heart attacks or stroke with nonselective NSAIDs could not be excluded.

In May 2015, according to the review evaluating the cardiovascular risks with systemic ibuprofen medicines, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) endorsed the proposal to update advice on the use of high-dose ibuprofen due to the confirmation of a small increased risk of cardiovascular problems, such as heart attacks and strokes, in patients taking high doses of ibuprofen (at or above 2,400 mg per day). The review clarified that the risk with high-dose ibuprofen is similar to the risk seen with some other non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors and diclofenac.

- Update of the SmPC and Package Leaflet of nonsteroidal anti-inflammatory drugs via systemic

In April 2007, AEMPS required to MAHs of one or more drugs that contain anti-inflammatory traditional drugs used via systemic to update the SmPC and Package Leaflet in relation to the new data on the cardiovascular, gastrointestinal and serious skin risks associated with these drugs (AEMPS, 2007).

- Identified and potential drug-drug interactions

In June 2008, the Pharmacovigilance Working Party published a report on Ibuprofen and low dose aspirin interaction Plan for implementation of agreed SmPC changes (sections 4.5 and 5.1).
Experimental data suggested that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly (PhVWP, 2008).

-Review to possible risks of pain medicine use during pregnancy

In January 2015, FDA evaluated research studies published in the medical literature and determined they were too limited to make any recommendations based on these studies at that time. Because of this uncertainty, the use of pain medicines during pregnancy should be carefully considered. It should be always recommended to pregnant women to discuss all medicines with their health care professionals before using them (FDA, 2015).

**Pseudoephedrine**

The available data of action taken by safety reasons since pseudoephedrine was marketed are as follows:

- Cough and cold medicines for children under 12 years

  On 1st April 2009, Medicines and Healthcare products Regulatory Agency (MHRA) concluded that cough and cold medicines containing the following active ingredients: antitussives (dextromethorphan and pholcodine); expectorants (guaifenesin and ipecacuanha); nasal decongestants (ephedrine, oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline); and antihistamines (brompheniramine, chlorphenamine, diphenhydramine, doxylamine, promethazine and triprolidine) should no longer be used in children under 6 years as the balance of benefits and risk had not been shown to be favourable.

  For children aged over 6 years, the risk from these ingredients is reduced because they suffer from cough and cold less frequently and consequently require medicines less often; with increased age and size, the risk of toxicity is lower; and they can say if the medicine is working (MHRA, 2009).

- Risk of illicit use

  In 2007, MHRA conducted a public consultation exercise on a proposal to reclassify over the counter (OTC) medicines containing pseudoephedrine or ephedrine to prescription only medicines (POM). On 1st April 2008, the following legal sales restrictions came into force:

  - It became illegal to sell or supply any product that contains more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription.
  - It became illegal to sell or supply a combination of products that between them add up to more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription.
  - It became illegal to sell or supply a product that contains pseudoephedrine and a product that contains ephedrine in one transaction.

**Ibuprofen/Pseudoephedrine combination**

As it has been commented, ibuprofen and pseudoephedrine combination tablets were approved for OTC use by adults in 1989 in the United States, and tablets and caplets have been marketed since that time. The first pediatric ibuprofen and pseudoephedrine combination suspension product was introduced for OTC marketing in September 2000 (FDA). In this way, the sponsor of Children’s Advil Cold Suspension Ibuprofen 100 mg/Pseudoephedrine hydrochloride 15 mg per 5 ml provided in their approval report a listing of serious cases for ibuprofen and pseudoephedrine combination products over the period 1989-2000, which corresponded to the initial marketing of the combination product.

56 serious cases were reported to involving the combination product. A total of 21 cases had MedDRA Terms consistent with allergic reactions. Twelve of these 21 cases involved single doses or doses of only two tablets in a single day. In two cases the age was unknown, and one case occurred in a 16-year old. In addition, five cases in adults involved angioneurotic oedema.
In a similar time period (between 1st January 1997 to 30th September 2000) 29 serious cases (all ages) were included in the FDA SRS and AERS databases for ibuprofen and pseudoephedrine combination products or for concomitant use of the single ingredient products (FDA, 2002).

The sponsor of Children’s MOTRIN Cold® Suspension also performed a post marketing surveillance in adults from 1st January 1994 to 31st December 1998 (FDA, 1999). In this period, 135 adverse events involving this combination were reported, of which twelve were considered to be serious by the reporting subject. All twelve serious reports required hospitalisation (one to five days) but none of them had a fatal outcome. Six of the twelve involved allergic reactions, including anaphylactoid reactions and angioedema, after a single dose of the combination product.

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

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC, as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety. Only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the patient information leaflet (PIL)) will be performed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the Competent Authority
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a Periodic Safety Update Report and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

**IV.7 Discussion on the clinical aspects**

The grant of a Marketing Authorisation is recommended for this application from a clinical viewpoint.

**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.

**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 pseudoephedrine hydrochloride 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 approved labelling for Ibuprofen and Pseudoephedrine hydrochloride Farmalider oral suspension is presented below.
## PARTICULARS TO APPEAR ON THE OUTER PACKAGING

### 1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen and Pseudoephedrine hydrochloride Fomalider 200 mg/30 mg/10 ml oral suspension

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition per ml:
- Ibuprofen, 20 mg/ml
- Pseudoephedrine hydrochloride, 3 mg/ml

### 3. LIST OF EXCIPIENTS

Excipients:
- Glycerol (E-422), 50 mg; maltitol, 500 mg; sodium, 2.68 mg; and other excipients.
  - See package leaflet for further information.

### 4. PHARMACEUTICAL FORM AND CONTENTS

- Oral suspension
- Bottle of 150 ml
- Bottle of 200 ml

### 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

- N/A

### 8. EXPIRY DATE

- EXP.

### 9. SPECIAL STORAGE CONDITIONS

### 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

Farmalider, S.A.
C/ La Granja, n°1, 3rd floor
28108, Alcobendas (Madrid)
Spain

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

Ibuprofen and Pseudoephedrine hydrochloride Farmalider is indicated for the relief of symptoms of cold and flu with associated pain, fever, congestion and runny nose, in adults and adolescents of 12 years and older.

Do not take if you:
- Have (or have ever 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 75 mg.

Speak to a pharmacist/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.

Do not give to children under 12 years of age.

If symptoms persist or worsen or if the product is required for more than 10 days, consult a doctor.

Warning: Do not take more medicine than the label tells you to.

16. INFORMATION IN BRAILLE

Ibuprofen and
Pseudoephedrine HCl
200mg/30mg/10ml
oral susp.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not Applicable
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
LABELLING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ibuprofen and Pseudoephedrine hydrochloride Farmalider 200 mg/30 mg/10 ml oral suspension
Oral use

2. METHOD OF ADMINISTRATION

Oral use

3. EXPIRY DATE

EXP

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>-

BATCH

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Composition per ml:
Ibuprofen, 20 mg/ml
Pseudoephedrine hydrochloride, 3 mg/ml

Excipients:
Glycerol (E-422), 50 mg; maltitol, 500 mg; sodium, 2.68 mg; and other excipients.
See package leaflet for further information.

6. OTHER

Oral suspension
Bottle of 150 ml
Bottle of 200 ml
Annex 1

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

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