Public Assessment Report

Decentralised Procedure

Ibuprofene e pseudoefedrina Wick Pharma 200 mg/30 mg compresse rivestite con film

VFA2012
200mg/30mg film coated tablets

Applicant: WICK-Pharma-Zweigniederlassung der Procter & Gamble GmbH

IT Marketing Authorisation Number: 042745

Procedure number: IT/H/0331/001/DC

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Module 1

Information about the Initial Procedure

Product Name	**IT/H/0331/001/DC:** VFA2012 200mg/30mg film coated tablets (Ibuprofene e pseudoefedrina Wick Pharma 200mg/30mg film coated tablets)
Type of application	Generic, Article 10 (1)
Active Substance	Ibuprofen, pseudoephedrine hydrocloride
Form	Film coated tablets
Strength	200mg/30mg
MA Holder	WICK-Pharma-Zweigniederlassung der Procter & Gamble GmbH Sulzbacher Strasse 40, 65824 Schwalbach am Taunus, Germany
Reference Member State (RMS)	IT
Concerned Memember States (CMS)	AT, CZ, DE, EL, ES, HU, IE, PL, RO, UK
Procedure number	IT/H/0331/001/DC
Timetable	End of procedure: Day 210 – 06 February 2014

Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Italian version of the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.
Here is reported the English version of the SMPC approved at European level

1. NAME OF THE MEDICINAL PRODUCT

<Product name> 200mg/ 30mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 200 mg ibuprofen and 30 mg pseudoephedrine hydrochloride equivalent to 24.6 mg pseudoephedrine

Excipients with known effect:
Colouring agents tartrazine (E102, 0.47 mg/film-coated tablet) and sunset yellow FCF (E110, 0.07 mg/film-coated tablet). Soya lecithin (E322, 0.37 mg/film-coated tablet).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Yellow coloured, oval shaped, biconvex film-coated tablet (dimension: approx. 15.6 mm x 7.7 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief of nasal/sinus congestion with headache, fever and pain associated with the common cold and influenza.

<Product name> is indicated in adults and adolescents aged 15 and over.

4.2 Posology and method of administration

Posology
Adults and adolescents aged 15 and over:
1 tablet (equivalent to 200 mg ibuprofen and 30 mg pseudoephedrine hydrochloride) every 4-6 hours if necessary.
For more severe symptoms, 2 tablets (equivalent to 400 mg ibuprofen and 60 mg pseudoephedrine hydrochloride) every 6-8 hours if necessary, to a maximum total daily dose.

The maximum total daily dose of 6 tablets (equivalent to 1200 mg ibuprofen and 180 mg pseudoephedrine hydrochloride) must not be exceeded.
Treatment should not be continued for more than 5 days.
This combination product should be used where both, the decongestant action of Pseudoephedrine hydrochloride and the analgesic and/or anti-inflammatory action of Ibuprofen, are required. If one symptom (*either* nasal congestion *or* headache and/or fever) predominates, single-agent therapy is preferable.

In older people and patients with a history of ulcers, particularly if complicated by haemorrhage or perforation (see section 4.3), start with lowest dose possible as the risk of gastrointestinal haemorrhage, ulceration or perforation is higher with increased doses of NSAIDs.
The concomitant use of protective agents (misoprostol or proton pump inhibitors) should be considered for these patients or patients taking other drugs that can increase the risk of gastrointestinal events (see below and section 4.5).

For patients with kidney or liver disorders it is necessary to adapt the dosage to suit the individual.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms.

Paediatric population

<Product name> is contraindicated in children under 15 years old (see section 4.3).

Method of administration
For oral use.
Tablets should be swallowed with water, preferably on a full stomach. Do not break or crush the tablets.

4.3 Contraindications

- Hypersensitivity to ibuprofen, pseudoephedrine or to any of the excipients listed in section 6.1.
- Patients aged under 15 years
- Pregnancy and Lactation (sees ection 4.6)
- A history of hypersensitivity reactions (e.g. bronchospasm, asthma, nasal polyposis, rhinitis, or urticaria) associated with aspirin, other analgesics, antipyretics or other non steroidal anti inflammatory drugs (NSAIDs).
- Active peptic ulcer or history of recurrent ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- History of gastrointestinal bleeding or perforation, including that associated with NSAIDs.
- Cerebrovascular or other bleeding.
- Unexplained haematopoietic abnormalities.
- Severe renal failure.
- Severe hepatic failure.
- Severe heart failure.
- Severe cardiovascular disorders, coronary artery disease (heart disease, hypertension, angina pectoris), tachycardia, hyperthyroidism, diabetes, phaeochromocytoma,
- History of stroke or presence of risk factors for stroke (because of the α-sympathomimetic activity of pseudoephedrine hydrochloride).
- Risk of closed-angle glaucoma.
- Risk of urinary retention related to urethroprostatic disorders.
- History of myocardial infarction.
- History of seizures.

- Disseminated lupus erythematosus.
- Concomitant use of other vasoconstrictor agents used as nasal decongestants, whether administered orally or nasally (e.g. phenylpropanolamine, phenylephrine and ephedrine), and methylphenidate (see section 4.5)
- Concomitant use of NSAIDs or aspirin with a daily dose above 75 mg, analgesics and COX 2 selective inhibitors (see section 4.5).
- Concomitant or prior use of monoamine oxidase inhibitors (MAOIs) in the preceding 2 weeks (see section 4.5).

4.4 Special warnings and precautions for use

Concomitant use of <Product name> with other NSAIDs containing cyclo-oxygenase (COX)-2 inhibitors should be avoided.

Undesirable effects may be reduced by using the minimum effective dose for the shortest duration necessary to control symptoms (see "Gastro-intestinal effects" and "Cardiovascular and cerebrovascular effects" below).

Special warnings related to pseudoephedrine hydrochloride:

- The dosage, the recommended maximum duration of treatment (5 days) and the contraindications must be strictly adhered to (see section 4.8).
- Patients should be informed that treatment must be discontinued if they develop hypertension, tachycardia, palpitations, cardiac arrhythmias, nausea or any neurological signs such as onset or worsening of headache.

Before using this product, patients should consult their doctor in case of:
- Hypertension, heart disease, hyperthyroidism, psychosis or diabetes.
- Concomitant administration of antimigraine agents, especially ergot alkaloid vasoconstrictors (because of the α-sympathomimetic activity of pseudoephedrine).
- SLE and mixed connective tissue disease: Systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis (see section 4.8).
- Neurological symptoms such as seizures, hallucinations, behavioural disturbances, agitation and insomnia have been described after systemic administration of vasoconstrictors, especially during febrile episodes or on overdose. These symptoms have been more commonly reported in paediatric population.

As a result, it is advisable:
- to avoid administration of (Invented name) either in combination with medicines which can lower the epileptogenic threshold, such as terpene derivatives, clobutinol, atropine-like substances and local anaesthetics, or where there is a history of seizures;
- to adhere strictly to the recommended dosage in all cases and to inform the patients about the risks of overdose if (Invented name) is taken concomitantly with other medicines containing vasoconstrictors.

Patients with urethroprostatic disorders are more prone to develop symptoms like dysuria and urinary retention.

Elderly patients may be more sensitive to the effects on the central nervous system (CNS).

Precautions for use related to pseudoephedrine hydrochloride:

- In patients undergoing scheduled surgery in which volatile halogenated anaesthetics are to be used, it is preferable to discontinue treatment with (Invented name) several days before surgery in view of the risk of acute hypertension (see section 4.5).
- Athletes should be informed that treatment with pseudoephedrine hydrochloride can lead to positive results in doping tests.

Interference with serological testing
Pseudoephedrine has the potential to reduce iobenguane i-131 uptake in neuroendocrine tumors, thus interfering with scintigraphy.

Special warnings related to ibuprofen:

Bronchospasm may be precipitated in patients suffering from, or with a history of bronchial asthma or allergic disease. The product should not be taken with cases of asthma without prior consultation with a doctor (see section 4.3).

Patients who have asthma associated with chronic rhinitis, chronic sinusitis and/or nasal polyposis have a higher risk of allergic reactions when taking acetylsalicylic acid and/or NSAIDs. Administration of (Invented name) may precipitate an acute asthma attack; particularly in some patients who are allergic to acetylsalicylic acid or an NSAID (see section 4.3).

Gastro-intestinal effects:
Gastro-intestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of gastrointestinal events.

The risk of gastro-intestinal bleeding, ulceration or perforation, which can be fatal, is higher with increasing NSAID doses, in patients with a history of ulcer (particularly if complicated with bleeding or perforation (see section 4.3) and in patients older than 60 years of age. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients and also for patients taking concomitant low-dose acetylsalicylic acid or other medicinal drug products likely to increase gastro-intestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, especially elderly patients, may present with un-usual abdominal symptoms (especially gastrointestinal bleeding) in the initial stages of treatment.

Particular caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding such as oral corticosteroids, anticoagulants such as warfarin, SSRIs or antiplatelet agents such as acetylsalicylic acid (see section *4.5*).

Treatment with <Product name> should be discontinued immediately if gastro-intestinal bleeding or ulceration occurs.
NSAIDs should be given with care to patients with a history of gastro-intestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Cardiovascular and cerebrovascular effects:
Clinical trials and epidemiological data suggest that use of ibuprofen, particularly at high doses (above 2400 mg daily) and in long-term treatment, may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke. Overall, epidemiological studies do not suggest that low-dose ibuprofen (below 1200 mg daily) is associated with an increased risk of myocardial infarction.

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention, hypertension or oedema have been observed in association with previous NSAID therapy; advice from a doctor and/or pharmacist must be sought prior to starting treatment under these circumstances.

Skin reactions:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see *section 4.8*). Patients are at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. <Product name> should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Precautions for use related to ibuprofen:
- Elderly: The pharmacokinetics of ibuprofen is not modified by age, no dose adjustments is necessary in the elderly. However, elderly patients should be carefully monitored as they are more sensitive to NSAID-related undesirable effects, particularly gastro-intestinal bleeding and perforation, which can be fatal.
- Caution and special monitoring is required when administering ibuprofen to patients with a history of gastro-intestinal disease (such as peptic ulcer, hiatus hernia or gastrointestinal bleeding).
- In the initial stages of treatment, careful monitoring of urine output and renal function is required in patients with heart failure, patients with chronically impaired renal or hepatic function, patients taking diuretics, patients who are hypovolaemic as a result of major surgery and, in particular, elderly patients. Renal function in these patients may be adversely influenced by treatment with NSAIDs.
- If visual disturbances occur during the course of treatment, a full ophthalmological examination should be carried out.

If symptoms persist or worsen, the patient should consult a doctor.

<Product name> contains 0.28 mg sodium per tablet.

<Product name> contains soya lecithin. If you are allergic to soya or peanut oil do not use this medicinal product.
<Product name> contains the azo colouring agents tartrazine (E102) and sunset yellow (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Combination of pseudoephedrine with:	**Possible Reaction**

Non-selective monoamine oxidase inhibitors (MAOIs):	<Product name> must not be taken by patients taking monoamine oxidase inhibitors (MAOIs) currently or in the last two weeks, since there is a risk of hypertensive episodes as paroxysmal hypertension and hyperthermia, which can be fatal (see section 4.3).
Other indirectly-acting, orally or nasally administered sympathomimetics or vasoconstrictor agents, α-sympathomimetic drugs, phenylpropanolamine, phenylephrine, ephedrine, methylphenidate:	Pseudoephedrine may potentiate the effect of other sympathomimetic (vasoconstrictor) and lead to risk of vasoconstriction and/or hypertensive crises.
Reversible inhibitors of monoamine oxidase A (RIMAs), linezolid, dopaminergic ergot alkaloids, vasoconstrictor ergot alkaloids:	Risk of vasoconstriction and/or hypertensive crises.
Volatile halogenated anaesthetics:	Perioperative acute hypertension. In scheduled surgery, discontinue treatment with <Product name> several days before.
Guanethidine, reserpine and methyldopa:	Effect of peudoephedrine may be diminished.
Tricyclic antidepressants:	Effect of peudoephedrine may be diminished or enhanced.
Digitalis, chinidine or tricyclic antidepressants:	Increased frequency of arrhythmia.

Concomitant use of ibuprofen with :	**Possible Reaction**
Other NSAIDs, salicylates, analgesics, antipyretics and COX 2:	The concomitant administration of several NSAIDs, analgesics, antipyretics and COX 2 selective inhibitors may increase the risk of adverse reactions as gastrointestinal ulcers and bleeding due to a synergistic effect. The concomitant use of with these products should therefore be avoided (see section 4.4).
Cardiac glycosides (as digoxin):	The concomitant use with digoxin preparations may increase serum levels cardiac glycosides (digoxin). A check of serum-digoxin is not as a rule required on correct use (maximum over 5 days).
Corticosteroids:	Corticosteriods as these may increase the risk of adverse reactions, especially of the gastrointestinal tract (gastrointestinal; ulceration or bleeding) (see section 4.3).
Anti-platelet agents:	Increased risk of gastrointestinal bleeding (see section 4.4).
Acetylsalicylic acid (low dose):	The concomitant administration of acetylsalicylic acid with a daily dose above 75 mg should be avoided due to increased risk of adverse reactions (see section 4.3).

Anticoagulants: (e.g.: warfarin, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, iloprost)	Increased risk of gastrointestinal bleeding as NSAIDs as ibuprofen may enhance the effect of anti-coagulants (see section 4.4)
Phenytoin:	The concomitant use of <Product name> with phenytoin preparations may increase serum levels of these medicinal products. A check of serum-phenytoin levels is not as a rule required on correct use (maximum over 5 days).
Selective serotonin reuptake inhibitors (SSRIs):	Increased risk of gastrointestinal bleeding (see section 4.4).
Lithium:	The concomitant use of <Product name> with lithium preparations may increase serum levels of these medicinal products. A check of serum-lithium is not as a rule required on correct use (maximum over 5 days).
Probenecid and sulfinpyrazone:	Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.
Diuretics, ACE inhibitors, betareceptor-blockers and angiotensin-II antagonists:	NSAIDs may reduce the effect of diuretics and other antihypertensive agents. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, betareceptor-blockers or angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.
Potassium sparing diuretics:	The concomitant administration of <Product name> and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).
Methotrexate:	The administration of (Invented name) within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.
Ciclosporin:	The risk of a kidney-damaging effect due to ciclosporin is increased through the concomitant administration of certain nonsteroidal antiinflammatory drugs. This effect also cannot be ruled out for a combination of ciclosporin with ibuprofen.
Tacrolimus:	The risk of nephrotoxicity is increased if the two medicinal products are administered concomitantly.

Zidovudine:	There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
Sulphonylureas:	Clinical investigations have shown interactions between nonsteroidal anti-inflammatory drugs and antidiabetics (sulphonylureas). Although interactions between ibuprofen and sulphonylureas have not been described to date, a check of blood-glucose values is recommended as a precaution on concomitant intake.
Quinolone antibiotics:	Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
Heparins; *Gingko biloba*:	Increased risk of bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy:

<Product name> is contraindicated during pregnancy (see section 4.3).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastrochisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 % , up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- Cardiopulmanary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction, which may progress to renal failure with oligo hydroamniosis;

The mother and the neonate, at the end of pregnancy, to:
- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- Inhibition of uterine contractions resulting in delayed or prolonged labour.

There is the possibility of an association between the occurrence of foetal abnormalities and the taking of pseudoephedrine in the 3rd trimester of pregnancy.

Breastfeeding

<Product name> is contraindicated during breast-feeding (see section 4.3).

Ibuprofen/pseudoephedrine have been identified in breastfed newborns/infants of treated women. There is insufficient information on the effects of ibuprofen/ pseudoephedrine in newborns/ infants.

Fertility

The effects of this product on fertility have not been specifically investigated.
The use of ibuprofen may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.
There are no adequate reproductive toxicology studies with pseudoephedrine.

4.7 Effects on ability to drive and use machines

<Product name> has no known effects on the ability to drive and use machines.
However, since dizziness or hallucinations may appear in exceptional cases, owing to the presence of pseudoephedrine, anyone intending to drive should take this possibility into account.

4.8 Undesirable effects

The most commonly-observed adverse events related to ibuprofen are gastrointestinal in nature. In general, the risk of development of adverse events (in particular the risk of development of serious gastrointestinal complications) increases with increasing dose and with increasing duration of treatment administration.
Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of:
(a) Non-specific allergic reaction and anaphylaxis
(b) Respiratory tract reactivity comprising of asthma, aggravated asthma, bronchospasm or dyspnoea
(c) Assorted skin disorders, including rashes of various types, pruritis, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme)
In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea,vomiting, fever or disorientation have been observed.
Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.
Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke), (see section 4.4).
The following list of adverse effects relates to those experienced with ibuprofen and pseudoephedrine hydrochloride at OTC doses, for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.
Patients should be informed that they should stop taking <Product name> immediately and consult a doctor if they experience a serious adverse drug reaction.

Adverse reaction frequency is defined using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Infections and infestations	Ibuprofen	Very rare	Exacerbation of infectious inflammations (e.g. necrotizing fasciitis), Aseptic meningitis (stiffness of the neck, headache, nausea, vomiting, fever or disorientation in patients with pre-existent autoimmune diseases (SLE, mixed connective tissue disease)
Blood and lymphatic system disorders	Ibuprofen	Very rare	Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis, neutropenia)

Immune system disorders	Ibuprofen	Uncommon	Hypersensitivity reactions with urticaria, pruritus, , skin rashes and asthma attacks (with drop in blood pressure)
	Ibuprofen and pseudoephedrine hydrochloride	Very rare	Severe generalised hypersensitivity reactions, signs may be facial oedema, angioedema, dyspnoea, bronchospasm, tachycardia, drop in blood pressure, anaphylactic shock
Psychiatric disorders	Ibuprofen	Very rare	Psychotic reactions, depression
	Pseudoephedrine hydrochloride	Not known	Agitation, hallucination, anxiety, abnormal behaviour, insomnia
Nervous system disorders	Ibuprofen	Uncommon	Central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness
	Pseudoephedrine hydrochloride	Rare Not known	Insomnia, nervousness anxiety, restlessness, tremor, hallucinations Haemorhagic stroke, ischemic stroke, convulsion, headache
Eye disorders	Ibuprofen	Uncommon	Visual disturbances
Ear and labyrinth disorders	Ibuprofen	Rare	Tinnitus
Cardiac disorders	Ibuprofen	Very rare	Oedema, hypertension, palpitations, heart failure, myocardial infarction
	Pseudoephedrine hydrochloride	Not known	Palpitations, tachycardia, chest pain, arrythmia
Vascular disorders	Ibuprofen	Very rare	Arterial hypertension
	Pseudoephedrine hydrochloride	Not known	Hypertension
Respiratory, thoracic and mediastinal disorders	Pseudoephedrine hydrochloride	Rare	Exacerbation of asthma or hypersensitivity reaction with bronchospasm
Gastrointestinal disorders	Ibuprofen	Common	Gastrointestinal discomfort, dyspepsia, abdominal pain, nausea, vomiting, flatulence, diarrhoea, anorexia, constipation, minor gastrointestinal blood loss in rare cases leading to anaemia
	Ibuprofen	Uncommon	Peptic ulcer, perforation, or gastrointestinal haemorrhage (with melaena or haematememesis, gastritis, ulcerous stomatitis. Exacerbation of colitis and Crohn's disease (see section 4.4)
	Ibuprofen	Very rare	Oesophagitis, pancreatitis, intestinal diaphragm-like stricture
	Pseudoephedrine hydrochloride	Not known	Dry mouth, thirst, nausea, vomiting
Hepatobiliary disorders	Ibuprofen	Very rare	Hepatic dysfunction, hepatic damage, particularly in long-term therapy, hepatic failure, acute hepatitis
Skin and subcutaneous tissue disorders	Ibuprofen	Uncommon	Various skin rashes
	Ibuprofen	Very rare	Severe forms of skin reactions as exfoliative dermatitis or bullous exanthema such as Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis (Lyell syndrome), alopecia, severe skin infections, soft-tissue complications in a varicella infection

	Pseudoephedrine hydrochloride	Not known	Rash, urticaria, pruritus,, erythema, hyperhidrosis
Renal and Urinary disorders	Ibuprofen	Rare	Kidney-tissue damage (papillary necrosis) and elevated uric acid concentrations in the blood
	Ibuprofen	Very rare	Renal and hepatic disorders, increase in serum creatinine, liver disorders, oedemas (particularly in patients with arterial hypertension or renal insufficiency), nephrotic syndrome, interstitial nephritis, acute renal insufficiency
	Pseudoephedrine hydrochloride	Not known	Urinary retention in men with prostatic hypertrophy

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system .

4.9 Overdose

Symptoms

The most frequent manifestations of ibuprofen overdose are abdominal pain, nausea, vomiting, lethargy, thirst, muscle weakness, drowsiness, blurred vision and dizziness. Other effects including headache, tinnitus, CNS depression, convulsions, hypotension, bradycardia, tachycardia, supraventricular and ventricular arrhythmias, and atrial fibrillation, may occur. Metabolic acidosis, coma, acute renal failure, hyperkalemia, apnoea (mainly in young children), respiratory depression, and respiratory failure have been reported rarely. Exacerbation of asthma is possible in asthmatics.

Symptoms and signs of pseudoephedrine overdose include irritability, insomnia, fever, sweating, anxiety, restlessness, tremor, convulsions, palpitations (sinus arrhythmia), hypertension, dry mouth, and difficulty in urination. Hallucinations have been reported (more likely in children).

Treatment

Treatment of overdose is supportive. Gastric lavage and activated charcoal may be of benefit within 1 hour of ingestion of a potentially toxic amount, and if necessary, correction of serum electrolytes.

Symptomatic and supportive treatment should be undertaken, particularly with regard to the cardiovascular and respiratory systems. For example, severe hypertension may need to be treated with an alpha-receptor blocking drug, whilst a beta-receptor blocking drug may be required to control cardiac arrhythmias. Convulsions may be controlled with intravenous diazepam, while chlorpromazine may be used to control marked excitement and hallucinations.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cold combination preparations; nasal decongestants for systemic use, sympathomimetics, pseudoephedrine combinations.
ATC code: R05X; R01BA52

<Product name> 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 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.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

Only limited toxicity data are available with the drug combination ibuprofen and pseudoephedrine hydrochloride.

Based on different mechanisms of action of ibuprofen (non-steroidal anti-inflammatory) and pseudoephedrine hydrochloride (sympathomimetic), a compound-specific toxicity profile related to the pharmacodynamic activity of the mono-compounds was seen in non-clinical toxicity tests

following overdosing (pseudoephedrine human data). Accordingly, there were different toxicological target organs, e.g. gastrointestinal lesions for ibuprofen and hemodynamic as well as CNS-effects for pseudoephedrine hydrochloride. Co-administration of ibuprofen and pseudoephedrine hydrochloride did not result in any clinically significant interaction. Therefore, no additive, synergistic and potentiating effects will be expected for the fixed-dose combination (FDC) ibuprofen/pseudoephedrine hydrochloride (200 mg/30 mg) in animals and men at equipotent doses. This is also supported by the absence of competitive metabolic pathways. There is no scientific evidence that the safety margins for the individual drugs will be different for the drug combination.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Microcrystalline cellulose
Pregelatinised starch (maize)
Povidone K-30
Colloidal anhydrous silica
Stearic acid 95
Crosscarmellose sodium
Sodium laurilsulfate
Film coating:
Polyvinyl Alcohol – Part. Hydrolyzed
Talc (E553b)
Titanium Dioxide (E 171)
Macrogol 3350
Tartrazine Aluminum Lake (E102)
Lecithin (soya) (E322)
Sunset Yellow FCF Aluminium Lake (E110)
MICA-Based Pearlescent Pigment
(Mixture of: Potassium aluminium silicate (E555)-[mica] and titanium dioxide (E171))
Polysorbate 80 (E433)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packs containing 12 tablets and consisting of a Polypropylene / Copolymer of polyethylene and cyclic olefines / polypropylene film and aluminium blister foil
or

blister packs containing 12 tablets and consisting of a Polyvinylchloride (PVC) / Aclar (Polychlorotrifluoroethylene (PCTFE) film and aluminium foil (25µm),
both packed in cardboard cartons.

Pack sizes: 12, 24 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

<[To be completed nationally]>

Module 3

Package Leaflets

In accordance with Directive 2010/84/EU, the Italian version of the package leaflet for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.
Here is reported the English version of the PIL approved at European level.

PACKAGE LEAFLET: INFORMATION FOR THE USER

<Product name> 200mg / 30mg film-coated tablets

Ibuprofen and Pseudoephedrine hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
This medicine is available without prescription. Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you.
- **Keep this leaflet**. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- You must talk to a doctor if you do not feel better or if you feel worse after 5 days.

What is in this leaflet

This medicine is called <Product name> 200mg / 30mg film-coated tablets but will be referred to as <Product name> throughout this leaflet.

1. WHAT <PRODUCT NAME> IS AND WHAT IT IS USED FOR

<Product name> contains the active substances ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), and pseudoephedrine, which is a nasal decongestant.
- Ibuprofen reduces pain, swelling and high temperature.
- Pseudoephedrine acts on the blood vessels in the nose to relieve nasal congestion.

<Product name> is indicated for the symptomatic relief of nasal congestion with headache, fever and/or pain associated with common colds and flu
<Product name> is indicated in adults and adolescent over 15 years.

Use this combination product only if you have blocked nose with pain or fever. Do not use this product if you have only one of these symptoms.

Talk to a doctor if you do not feel better or if you feel worse after 5 days.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE <PRODUCT NAME>

Do NOT take <Product name> if you:
- are allergic to ibuprofen, pseudoephedrine or any of the other ingredients in this medicine (listed in Section 6 and end of Section 2)
- are younger than 15 years
- are pregnant or breast feeding
- have ever had an allergic reaction (such as wheezing, worsening of asthma, itchy runny nose, facial swelling or hives) when previously taking aspirin or other painkillers, other fever-reducing or anti-inflammatory drugs
- have a stomach ulcer or have previously had stomach ulcers,
- have previously had perforation or bleeding related to taking NSAIDs
- have severe liver or kidney failure
- have severe heart failure
- have severe heart or circulation problems (heart disease, high blood pressure, angina, fast heart rate), an overactive thyroid gland, diabetes, phaeochromocytoma (a tumour of the adrenal gland)
- have history of heart attack (myocardial infarction)
- have uncontrolled high blood pressure
- have had a stroke or you are at risk of having a stroke
- have history of seizures
- have any unexplained blood disorders
- have glaucoma (pressure in the eye)
- have difficulty in urinating related to prostate problems
- have Systemic Lupus Erythematosus (LSE), an illness affecting the immune system causing e.g. joint pain and skin changes
- are taking:
  - aspirin (more than 75 mg a day) or other non steroidal anti-inflammatory drugs (NSAIDs) or other painkillers
  - other nasal decongestants as e.g. phenylpropanolamine, phenylephrine or ephedrine or methylphenidate
  - non-selective monoamine oxidase inhibitors (known as MAOIs and used in the treatment of Parkinson's disease or depression) or have taken them in the last 2 weeks

Do NOT give <Product name> to children under 15 years of age.

Warnings and precautions
Talk to your doctor or pharmacist **before** taking <Product name>:
- if you have asthma; risk of an asthma attack
- if you have been told by your doctor that you have a blood clotting disorder
- if you are taking medicines to thin the blood e.g. warfarin, low dose aspirin
- if you are taking medicines which could increase the risk of stomach ulcers or bleeding e.g. steroids, antidepressants of the selective serotonin-reuptake inhibitors (SSRI) class (e.g. fluoxetine, paroxetine) or NSAIDs including aspirin
- if you have high blood pressure, heart problems , heart failure, psychosis or diabetes
- if you have a history of gastrointestinal disease (such as ulcerative colitis or Crohn's disease)
- if you have kidney or liver problems
- if you are taking antimigraine agents.

Medicines such as <Product name> may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. **Do not exceed the recommended dose or duration of treatment.**

If you have heart problems, previously had a stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol, or if you are a smoker) you should discuss your treatment with your doctor or pharmacist.

You should avoid alcohol intake during the treatment.

Contact a doctor if symptoms persist or worsen.

Children and adolescents

<Product name> should not be given to children below 15 years.

Other medicines and <Product name>

Please tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription.

<Product name> must not be used if you are taking:
- aspirin (more than 75 mg a day)
- other non-steroidal anti-inflammatory drugs (NSAIDs)
- other painkillers or fever-reducing drugs
- or have taken in the last 2 weeks monoamine oxidase inhibitors (MAOIs used in the treatment of Parkinson's disease or depression)
- other vasoconstrictor agents used as nasal degongestants (e.g. phenylpropanolamine, phenylephrine and ephedrine, administered orally or nasally).

In particular tell your doctor or pharmacist if you are taking the following as their effects may be changed:
- medicines to thin the blood (anti-coagulants and anti-aggregants) e.g. warfarin or aspirin
- medicines which could increase the risk of stomach ulcers or bleeding e.g. steroids, antidepressants of the SSRI class (e.g. fluoxetine, paroxetine) or NSAIDs including aspirin and cyclo-oxygenase (COX)-2 selective inhibitors
- medicines for high blood pressure, irregular heart rhythm, angina, heart failure or fluid retention (e.g. ACE-inhibitors, betablockers, angiotensin II agonists, cardiac glycosides) because <Product name> may reduce their effects or increase the risk of abnormal heart rhythm, high blood pressure or impaired kidney function
- cyclosporin (an immunosuppressant) as there may be an increased risk of impaired kidney function
- medicines for depression (lithium, tricyclic antidepressants) may increase the risk of side effects
- concomitant use of phenytoin may increase serum levels of these medicinal products. A check of serum-phenytoin levels is not as a rule required on correct use (maximum over 5 days)
- other decongestants or medicines to reduce appetite as these may increase the risk of side effects
- probenecid or sulfinpyrazone may delay excretion of ibuprofen
- sulphonylureas (antidiabetics): although interactions with ibuprofen have not been described, a check of blood-glucose values is recommended as a precaution on concomitant intake
- medicines to increase urination (diuretics/ water tablets)
- methotrexate in high dose (over 20mg per week), as it may lead to elevated effect of methotrexate
- quinolone antibiotics due to increased risk of developing convulsions

- ciclosporin, tacrolimus and trimethoprim
- anti-migraine agents
- zidovudine (for treating HIV)
- injectable heparin or and preparations containing *Gingko biloba* due to increased risk of bleeding.

Due to pseudoephedrine administration an acute hypertensive response may develop in the perioperative period. Therefore, discontinue treatment with <Product name> several days before surgery and inform your anaesthetist.

<Product name> with food and drink
Swallow the tablets with water, preferably on a full stomach.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding or think you might be pregnant or planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

<Product name> must not be taken during pregnancy or if you are breast-feeding. The active ingredients, ibuprofen and pseudoephedrine, can cause serious problems in unborn children and have been shown to be present in breastfed infants of women who have taken them.

<Product name> contains ibuprofen which belongs to a group of medicines (NSAIDs) which may impair the fertility in women. This effect is reversible on stopping the medicine.

Driving and using machines
<Product name> has no known effects on the ability to drive and use machines. Dizziness or hallucinations may appear in exceptional cases and this possibility should be taken into account.

<Product name> contains:
- FD&C Yellow number 5/Tartrazine Aluminium Lake (E102, 0.47 mg/film-coated tablet) and FD&C Yellow number 6/Sunset Yellow FCF Aluminium Lake (E110, 0.07 mg/film-coated tablet) which are colouring agents and may cause allergic reactions
- Soya lecithin (E322, 0.37 mg/film-coated tablet) – if you are allergic to soya or peanut oil, do not use this medicinal product
- Sodium – this medicinal product contains 0.28 mg sodium per tablet. To be taken into consideration by those on a controlled sodium diet.

3. HOW TO TAKE <PRODUCT NAME>

Always take <Product name> exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

<Product name> is for oral use only.

The recommended dose is:
Adults and adolescents aged 15 and over: 1tablet every 4-6 hours as necessary. For more severe symptoms 2 tablets every 6-8 hours as necessary

Do not exceed the maximum daily dose of 6 tablets.

Swallow the tablets with water, preferably on a full stomach. Do not break or crush the tablets.

Use in children and adolescents
Do not give to children under 15 years of age.

Duration of treatment
This product is intended for short term use only. You should use the lowest dose for the shortest time necessary to relieve your symptoms. Do not take longer than 5 days.

If symptoms persist or worsen, consult your doctor.

If you take more <Product name> than you should
Seek medical advice immediately if you, or someone else, accidentally take more <Product name> than is recommended.

If you forget to take <Product name>
Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your pharmacist or doctor.

4. POSSIBLE SIDE EFFECTS

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

STOP TAKING <Product name> and **seek medical help immediately:**
- if you have any of the following which may be signs of a **severe allergic reaction:**
    - difficulty breathing or swallowing
    - swelling of face, lips, tongue or throat
    - severe itching of the skin with hives (nettle rash)
    - severe skin reactions involving blisters under the skin
    - heart racing with low blood pressure
- if you have signs of intestinal bleeding as
    - bright red faeces (stools/motions), black tarry stools, vomiting blood or dark particles looking like coffee grounds

Other side effects may include:

Common (may affect up to 1 in 10 people):
- stomach disorders such as abdominal discomfort, indigestion, nausea, vomiting, flatulence, diarrhoea, constipation

Uncommon (may affect up to 1 in 100 people):
- headache, dizziness, difficulty in sleeping, agitation, irritability or tiredness
- visual disturbances
- stomach pain or ulcer, sometimes with bleeding or perforation, worsening of colitis and Crohn's disease
- skin rashes

Rare (may affect up to 1 in 1,000 people):
- tinnitus
- headache, dizziness and hallucinations
- nervousness, tremor, hallucinations.
- kidney-tissue damage, elevated uric acid concentration in blood

Very rare (may affect up to 1 in 10,000 people):
- infectious inflammations, symptoms of meningitis (headache, fever, neck stiffness)

- blood disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding from the nose and bruising
- severe allergic reactions
- psychotic reactions, depression
- kidney failure or other kidney disorders
- liver disorders
- severe skin reactions.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system.. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE <PRODUCT NAME>

Keep this medicine out of the sight and reach of children.

This medicine does not require any special storage conditions.

Do not use <Product name> after the expiry date which is stated on the blister/carton after ”EXP”.The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What <Product name> contains

- The **active substances** are ibuprofen (200mg per tablet) and pseudoephedrine hydrochloride (30mg per tablet, equivalent to pseudoephedrine base 24.6 mg)
- The **other ingredients** are
  microcrystalline cellulose, pregelatinised starch (maize), povidone K-30, colloidal anhydrous silica, stearic acid 95, crosscarmellose sodium , sodium laurilsulfate, polyvinyl alcohol – part. hydrolyzed, talc (E553b), titanium dioxide (E171), macrogol 3350, /Tartrazine Aluminum Lake (E102), lecithin (Soya) (E322), Sunset Yellow FCF Aluminum Lake (E110), MICA-based pearlescent pigment (mixture of potassium aluminium silicate (E555)-[mica], titanium dioxide (E171)), polysorbate 80
  (See end of Section 2 for further information on colouring agents and sodium).

What <Product name> looks like and contents of the pack

<Product name> tablets are yellow coloured, oval shaped film-coated tablets (dimension: approx. 15.6 mm x 7.7 mm).

The tablets are available in blister packs of 12 or 24 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

<This medicinal product is authorised in the Member States of the EEA under the following names:>

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>
<[To be completed nationally]>

This leaflet was last revised in {MM/YYYY}.

<[To be completed nationally]>

Module 4

Labelling

INNER LABELLING

1.3.1 Labelling

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

<Product name> 200mg / 30mg film-coated tablets

Ibuprofen and pseudoephedrine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

3. EXPIRY DATE

<[To be completed nationally]>

4. BATCH NUMBER

<[To be completed nationally]>

5. OTHER

OUTER LABELLING

1.3.1 Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1.

1. NAME OF THE MEDICINAL PRODUCT

<Product name> 200mg / 30mg film-coated tablet

Ibuprofen and pseudoephedrine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains:
200mg ibuprofen
30mg pseudoephedrine hydrochloride (equivalent to 24.6mg pseudoephedrine)

3. LIST OF EXCIPIENTS

Each film-coated tablet contains also colouring agents E102 (0.47 mg) and E110 (0.07 mg). Soya lecithin E322 (0.37 mg).

4. PHARMACEUTICAL FORM AND CONTENTS

12 film-coated tablets
24 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

<[To be completed nationally]>

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

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

<[To be completed nationally]>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription.
<[To be completed nationally]>

15. INSTRUCTIONS ON USE

<Product name> is indicated for the symptomatic relief of nasal congestion with headache, fever and/or pain in adults and adolescents aged 15 and over suffering from common cold and influenza.

Directions:
Adults and adolescents aged 15 and over: 1 every 4-6 hours as necessary. For more severe symptoms 2 tablets every 6-8 hours as necessary.
Do not exceed maximum daily dose of 6 tablets.

Swallow the tablets with water, preferably on a full stomach. Do not break or crush the tablets.

Do not give to children and adolescents under 15 years of age. Do not take if you are pregnant or breast-feeding.

Do not take longer than 5 days.
If symptoms persist or worsen, contact your doctor.

16. INFORMATION IN BRAILLE

<[To be completed nationally]>

Module 5

Scientific discussion during the initial procedure

I. Introduction

Based on the review of the data on quality, safety and efficacy, all the member states involved in the procedure considers that the application for VFA-2012 Ibuprofen/Pseudoephedrine hydrochloride 200mg/30mg in the "Symptomatic relief of nasal/sinus congestion with headache, fever and pain associated with the common cold and influenza" indicated in adults and adolescents aged 15 and over (MA No 042745; Procedure No IT/H/0331/001/DC) could be approved.

This decentralised application concerns a generic version of Ibuprofen/Pseudoephedrine hydrochloride, under VFA2012 trade name.
The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Nurofen Cold & Flu / Nurofen Sinus Relief, 200mg/30mg, Film-coated tablets by Reckitt Benckiser Healthcare (UK) Ltd licenced in UK since 1993-11-24.
The originator product is Nurofen Influenza e Raffreddore, 200mg/30mg coated tablets by Reckitt Benckiser Healthcare International Ltd – 103-105 Bath Road, Slough, Berkshire, SL1 3UH (UK) authorised via national procedure in 1999-02-03.

VFA2012 is a medicine consisting of a combination of two active substances: ibuprofen and Pseudoephedrine (ATC code: R05XR01BA52).
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 nonsteroidal 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.

To support the application, a bioequivalence study was submitted: "An Open-Label, Balanced, Randomised, Two-Treatment, Two-period, Two-Sequence, Single Oral Dose, Two Way Crossover, Bioequivalence Study Of Two Formulations Of Ibuprofen 200 Mg And Pseudoephedrine Hydrochloride 30 Mg Tablets In Healthy Adult Human Subjects Under Fasting Conditions". The test product was compared with reference product Nurofen Influenza e Raffreddore tablets.
The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The Reference Member States (RMS) has been assumed that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For
manufacturing sites within the Community, the RMS has accepted copies of competent manufacturer authorization issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites

.

II. About the product

Proposed name of the medicinal product in the RMS	**Ibuprofene e pseudoefedrina Wick Pharma 200 mg/30 mg compresse rivestite con film**
Name of the drug substances (INN name):	Ibuprofen/Pseudoephedrine hydrochloride
Pharmaco-therapeutic group (ATC Code):	Pharmacotherapeutic group: Other cold combination preparations; nasal decongestants for systemic use, sympathomimetics, pseudoephedrine combinations. ATC code: R05X; R01BA52
Pharmaceutical form(s) and strength(s):	Film Coated Tablet 200 mg/ 30 mg
Reference Number(s) for the Decentralised Procedure	IT/H/0331/001/DC
Reference Member State:	IT
Concerned Member States:	AT, CZ, DE, EL, ES, HU, IE, PL, RO, UK
Marketing Authorisation Numbers	AIC No:
Name and address of the Authorization Holder	WICK-Pharma-Zweigniederlassung der Procter & Gamble GmbH Sulzbacher Strasse 40, 65824 Schwalbach am Taunus, Germany

III. Scientific Overview and discussion

III.1 Quality aspects

ACTIVE SUBBSTANCE - IBUPROFEN

INN: Ibuprofen

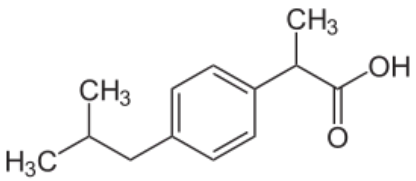
Chemical Name: ((2RS)-2-[4-(2-Methylpropyl)phenyl]propanoic acid.

Molecular Formula: $C_{13}H_{18}O_2$

CAS number: 15687-27-1

The **Ibuprofen** drug substance is a white or almost white, crystalline powder or colourless crystals, practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates. Ibuprofen has a chiral center and two enantiomers,(S) isomer and (R) isomer and it is a racemic mixture of the two isomers.
The chemistry, manufacturing and controls information for the specifications (tests, references to analytical procedures and acceptance criteria) of Ibuprofen drug substance has been evaluated by EDQM for the grant of European Certificate of Suitability

Structure:



Molecular weight: 206.3 g/mol
Appearance: white or almost white, crystalline powder or colourless crystals.
Solubility: practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

Ibuprofen has a chiral center and two enantiomers,(S) isomer and (R) isomer and it is a racemic mixture of the two isomers.

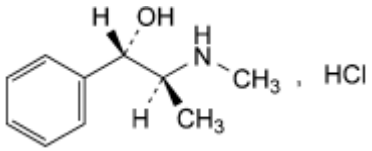
Ibuprofen is the subject of a European Pharmacopoeia monograph (n°0721)

All aspects of the manufacture and control of the active substance Ibuprofen, except for the proposed packaging specifications and stability data are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.
Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

ACTIVE SUBSTANCE: PSEUDOEPHEDRINE HYDROCHLORIDE

INN:	Pseudoephedrine Hydrochloride
Chemical Name:	(1S,2S)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride
Molecular Formula:	$C_{10}H_{16}ClNO$
CAS number:	345-78-8

Structure:



Molecular weight: 201.7 g/mol

Appearance: white or almost white, crystalline powder or colourless crystals
Solubility: freely soluble in water and in ethanol (96 per cent), sparingly soluble in methylene chloride;
melting point: about 184 °C

Pseudoephedrine Hydrochloride is the subject of a European Pharmacopoeia monograph. (n° 1367)

All aspects of the manufacture and control of the active substance Pseudoephedrine Hydrochloride, except for the proposed packaging specifications and stability data are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

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

DRUG PRODUCT

Ibuprofen and Pseudoephedrine Hydrochloride film coated tablets are intended for the relief of symptoms of cold and influenza such as nasal and sinus congestion, aches and pains, fever, and headache.
The medicinal product is presented as yellow, oval shaped, biconvex, film-coated tablets.
All the excipients of the core tablet also comply with the requirements of the relevant Ph.Eur. monographs and are all well established and are commonly used in pharmaceutical products of this type.

Other Ingredients

Tablet Core:
Microcrystalline cellulose, Pregelatinised starch (maize), Povidone K-30, Colloidal anhydrous silica, Stearic acid 95, Croscarmellose sodium, Sodium laurilsulfate

Film coating:
Polyvinyl Alcohol – Part. Hydrolyzed, Talc (E553b), Titanium Dioxide (E 171), Macrogol 3350 FD&C Yellow (E102) Lecithin (soya) (E322), FD&C Yellow (E110), MICA-Based Pearlescent Pigment (Mixture of: Potassium aluminium silicate (E555)-[mica] and titanium dioxide (E171)) , Polysorbate 80 (E433).
All the excipients comply with their respective European Pharmacopeia monographs.
The qualitative formulation was developed and each of the excipients was selected for its intended use based on optimization studies. They are included in the formulation at suitable levels and for recognized purposes.

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

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

Pharmaceutical Development

To seek essential similarity to the innovator product and to have a product similar in in-vivo performance to innovator product, strategy was to develop formulations of Ibuprofen and Pseudoephedrine Hydrochloride film coated tablets which is bioequivalent to the reference product of Nurofen Influenza e Raffreddore manufactured by Reckitt Benckiser Healthcare International.

Suitable pharmaceutical development data has been provided for these applications

Satisfactory comparative *in-vitro* dissolution and impurity profiles have been provided for the applicant's proposed product and its respective reference product.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been adequately validated.

Control of Finished Product
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container Closure System
The tablets are packaged in blister packs containing 12 tablets and consisting of a Polypropylene / Copolymer of polyethylene and cyclic olefines/polypropylene film and aluminium blister foil or blister packs containing 12 tablets and consisting of a Polyvinylchloride (PVC) / Aclar (Polychlorotrifluoroethylene (PCTFE) film and aluminium foil (25µm), both packed in cardboard cartons.
Pack sizes: 12, 24 film-coated tablets
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

Stability
Finished product stability studies were performed according to the current ICH stability guideline guidelines on batches of finished product packed in the packaging proposed for marketing.
Based on the results, a shelf-life of 3 years has been justified
The tablets will be packed in two different blisters: PVC/PCTFE and PP/COC/PP and Aluminium foil

III.2 Non-clinical aspects

Ibuprofen and pseudoephedrine hydrochloride have been in worldwide clinical use as single agents and in combination drug products for decades. There is sufficient well documented clinical experience of their use in fixed combination to establish all aspects of clinical efficacy and safety. Therefore, there is no requirement for any nonclinical combination investigations; this is in accordance with the principles for compounds already approved as combination therapy, as detailed in the CHMP Guideline on the Nonclinical Development of Fixed Combinations of Medicinal

Products EMEA/CHMP/SWP/258498/2005).
Overview based on literature review is, thus, appropriate
The environmental risk assessment **(ERA)** has been performed based on literature and summaries. Risk evaluation has been performed for the single compound based on the maximum daily doses in accordance with the EMEA/CHMP/SWP/4447/00corr 1 guideline.

III.3 Clinical aspects

The Clinical pharmacology of ibuprofen and Pseudoephedrine is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

Pharmacokinetics
In support of the application, the Marketing Authorisation Holder submitted the following bioequivalence study:

One single-dose, bioequivalence study, comparing the test product Ibuprofen 200 mg and Pseudoephedrine Hydrochloride 30 mg Tablets (Procter & Gamble GmbH)with the reference product Nurofen Influenza E Raffreddore tablets- (Reckitt Benckiser Healthcare International), containing fixed dose combination of ibuprofen 200 mg and Pseudoephedrine Hydrochloride 30 mg. The study was conducted in healthy, adult, human subjects under fasting condition.

S-ibuprofen has the majority of beneficial therapeutic activity for ibuprofen acceptance criteria for assessing bioequivalence. The pharmacokinetic results showed that bioequivalence was achieved for each pharmacokinetic parameter for both ibuprofen isomers and also for total (R+S)-ibuprofen, and for pseudoephedrine.

EFFICACY
The efficacy of Ibuprofen and Pseudoephedrine is well-known. No new efficacy data have been submitted and none are required for applications of this type.

SAFETY
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence study.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN

A summary of Pharmacovigilance System has been presented. It, as decsribed by the applicant fulfils teh requirements and provide adequate evidence that the applicant has the services of a qualified person repsponsible for pharmacovigilance and has the necessary means for the notiication of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable EU-Risk Management plan has been provided for this product. According to the “Module V- RMP” and the “Guidance on format of the RMP in the EU for Generics” RMP modules SI-SVII may be omitted for Generic Products. The RMP submitted has been approved

SUMMARY OF PRODUCT CHARACTERISTICS (Sm.PCs), PATIENT INFORMATION LEAFLETS (PILs) AND LABELLING

The SmPCs, PILs and labelling are acceptable from a clinical perspective. The SmPC is consistent with those for the originator products. The PIL is consistent with the details in the SmPC and both are in-line with the current guidelines. The labelling is in-line with current guidance.
The package leaflet has been evaluated via 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 the user testing PIL was English

IV Overall conclusions and benefit-risk assessment

The quality characteristics VFA2012 200mg/30mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch.

No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of Ibuprofen and pseudoephedrine hydrochloride are well-known, no additional data were required.
From the non-clinical point of view no safety concerns have been identified

With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.
Bioequivalence has been demonstrated between the test product ibuprofen 200 mg and Pseudoephedrine Hydrochloride 30 mg Tablets (Procter & Gamble GmbH) and the reference product Nurofen Influenza E Raffreddore tablets- (Reckitt Benckiser Healthcare International)

With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profiles of Ibuprofen and Pseudoephedrine are well known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence study.

The SmPC, PIL and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFITI RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Two post approval commitments related to quality aspects have been agreed

Bioequivalence between the test product Ibuprofen and Pseudoephedrine Hydrochloride Wick Pharma 200 mg /30 mg Tablets (Procter & Gamble GmbH) versus the reference product Nurofen Influenza E Raffreddore tablets- (Reckitt Benckiser Healthcare International) has been demonstrated.

Extensive clinical experience with Ibuprofen and Pseudoephedrine is considered to have demonstrated the therapeutic value of the products.
The benefit/risk balance is, therefore, considered to be positive