Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Advil Cold & Flu Relief Soft Capsules Ibuprofen 200mg Pseudoephedrine Hydrochloride 30mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substances	**mg/capsule**
Ibuprofen	200
Pseudoephedrine Hydrochloride	30

Excipients with known effect: Sorbitol (E 420), soya lecithin.

3 PHARMACEUTICAL FORM

Soft capsules (capsules).

A clear, oval, soft-gelatin capsule filled with a clear liquid and printed with 200/30 in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Advil Cold & Flu Relief is indicated for the relief of symptoms of the common cold and flu such as headache, fever, sore throat, minor aches and pain when associated with blocked nose (nasal congestion) and sinuses (sinusitis) in adults and adolescents over 12 years of age.

4.2 Posology and method of administration

For oral administration and short-term use only.

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.

Posology

Adults, older people and adolescents over 12 years of age:
Take 1 capsule every 4-6 hours to a maximum of 6 capsules in any 24 hour period.

In case of more intense symptoms, 2 capsules (400 mg ibuprofen/60 mg pseudoephedrine hydrochloride) may be taken at a time. The dose can be repeated, if necessary, at six-hour intervals without exceeding a maximum daily dose of 6 capsules (1200 mg of ibuprofen and 180 mg of pseudoephedrine hydrochloride).

The lowest effective dose should be used for the shortest duration necessary to relieve the symptoms (see section 4.4).

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4). Maximum duration of treatment is 5 days unless instructed otherwise by a doctor.

Paediatric population

Advil Cold & Flu Relief is contraindicated in children under the age of 12 years.

Renal and hepatic insufficiency

No dose reduction is required in patients with mild to moderate renal or hepatic impairment. (see section 4.4) The lowest effective dose should be used.

Method of administration

For oral administration only. Capsules should be taken with a glass of water.

4.3 Contraindications

Hypersensitivity to the active substances to peanut or soya or to any of the excipients listed in section 6.1.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, bronchospasm, rhinitis, angioedema, urticaria), in response to ibuprofen, acetylsalicylic acid or other non- steroidal anti-inflammatory drugs.

Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

History of gastrointestinal bleeding or perforation, related to previous NSAID therapy.

Patients with severe heart failure (NYHA Class IV), renal failure or hepatic failure (See section 4.4).

During pregnancy and breast-feeding (See section 4.6).

Use in children under 12 years of age.

Patients with serious cardiovascular disease, tachycardia, hypertension, severe renal impairment, angina pectoris, hyperthyroidism, diabetes, phaeochromocytoma, closed angle glaucoma, prostatic enlargement**.**

Patients taking other NSAIDs including cyclooxygenase-2 selective inhibitors, pain relievers or decongestants.

Patients receiving tricyclic antidepressants.

Patients currently receiving, or who have within the last two weeks received, monoamine oxidase inhibitors.

4.4 Special warnings and precautions for use

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see GI and cardiovascular risks below).

If symptoms worsen, do not improve or patients experience any other symptoms not related to the original condition, treatment should be stopped and patients should be instructed to consult a doctor or healthcare professional.

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.8)

Patients suffering from asthma, hypertension, heart disease, diabetes, liver cirrhosis, renal or hepatic impairment, thyroid disease or prostatic hypertrophy should consult their doctor before using this product. (See section 4.3 and 4.8)

Consumption of alcohol should be avoided during treatment.
Pseudoephedrine hydrochloride may cause a positive reaction in tests conducted during anti-doping checks.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicine contains 64.1 mg of sorbitol in each capsule which is equivalent to 69.7 mg/g.

Severe Skin reactions

Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) may occur with ibuprofen and pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of Advil Cold & Flu Relief Capsules should be discontinued and appropriate measures taken if needed.

Ischaemic optic neuropathy
Ischaemic optic neuropathy has been reported with pseudoephedrine. Pseudoephedrine should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

Masking of symptoms of underlying infections
Advil Cold & Flu Relief can mask symptoms of infection, which may lead to a delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications of varicella. When Advil Cold & Flu Relief is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non. hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Other NSAIDs:	The use of Advil Cold & Flu Relief with concomitant NSAIDs including cyclo-oxygenase-2 selective inhibitors should be avoided (see section 4.3 and 4.5).
Respiratory:	Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.
Systematic Lupus Erythematosus and mixed connective tissue disease:	Increase risk of aseptic meningitis (see section 4.8)
Renal effects:	In patients with cardiac or renal dysfunction, caution is required since the use of NSAIDs may result in deterioration in renal function. (see sections 4.3 and 4.8)
Hepatic effects:	Hepatic dysfunction (see sections 4.3 and 4.8)
Cardiovascular and cerebrovascular effects:	Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/ day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. $\leq$1200 mg day) is associated with an increased risk of arterial thrombotic events. Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided. Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required. As NSAIDs can interfere with platelet function, they should be used with caution in patients with intra-cranial haemorrhage and bleeding diathesis.
Gastrointestinal effects:	NSAIDs should be given with care to patients with a history of gastrointestinal disease (e.g. ulcerative colitis and Crohn's disease) as their condition may be exacerbated (see sections 4.8).

	GI 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 serious GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. 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 requiring concomitant low dose acetylsalicylic acid or other drugs likely to increase gastrointestinal risk (see below and 4.5) Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5). When GI bleeding or ulceration occurs in patients receiving this medicinal product, the treatment should be withdrawn. <u>Ischaemic colitis</u> Some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.
Dermatological:	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 appear to be at highest risk for 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. Advil Cold & Flu Relief should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Exceptionally, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections

	cannot be ruled out. Thus, it is advisable to avoid use of Advil Cold & Flu Relief Capsules in case of varicella.
Paediatric:	There is a risk of renal impairment in dehydrated adolescents or young persons, between the age of 12 and 18 years.

4.5 Interaction with other medicinal products and other forms of interaction

It is considered unsafe to take Ibuprofen in combination with warfarin or heparin unless under direct medical supervision.

Not recommended combinations:

Acetylsalicylic acid

Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce thecardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (seesection 5.1).

Combinations requiring precautions:

Care should be taken in patients treated with any of the following drugs as interactions have been reported.

Related to the presence of pseudoephedrine hydrochloride:

Combination of pseudoephedrine with:	**Possible Reaction**
Non-selective MAOIs (iproniazid):	This product should not be taken by patients who are currently or in the previous two weeks have taken monoamine oxidase inhibitors (MAO inhibitors) because the risk of a hypertensive episode as paroxysmal hypertension, hyperthermia can lead to death(see section 4.3).
Other indirectly-acting, orally or nasally administered sympathomimetics or vasoconstrictor agents, α-sympathomimetic drugs, phenylpropanolamine, phenylephrine, ephedrine, methylphenidate:	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 acute hypertensive episode
Volatile halogenated anaesthetics:	Perioperative acute hypertension. In scheduled surgery, discontinue treatment with (Trade Name) several days before.
Guanethidine, reserpine and methyldopa:	Effect of pseudoephedrine may be diminished or enhanced
Tricyclic antidepressants:	Effect of pseudoephedrine may be diminished or enhanced.
Digitalis, quinidine or tricyclic antidepressants:	Increased frequency of arrhythmia.

Related to the presence of ibuprofen:

Concomitant use of ibuprofen with :	**Possible Reaction**
Other NSAIDs including cyclooxygenase-2 selective inhibitors:	The concomitant administration of two or more NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. The concomitant use of ibuprofen with other NSAIDs should therefore be avoided (see sections 4.3 and 4.4).

Anti-platelet agents: (e.g. warfarin, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, iloprost)	Increased risk of gastrointestinal bleeding (see section 4.4).
Acetylsalicylic acid:	Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects. Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).
Anticoagulants:	NSAIDs such as ibuprofen may enhance the effect of anti-coagulants (see section 4.4).
Lithium:	The concomitant use of Advil Cold & Flu Relief 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).
Selective serotonin reuptake inhibitors (SSRIs):	Increased risk of gastrointestinal bleeding (see section 4.4).
Methotrexate:	The administration of Advil Cold & Flu Relief within 24 hours before or after administration of methotrexate may lead to elevated concentrations of plasma methotrexate and an increase in its toxic effect.
Diuretics, ACE inhibitors, beta-receptor blockers and angiotensin-II antagonists:	NSAIDs may reduce the effect of diuretics and other antihypertensive medicinal products. 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, beta receptor-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 (decreased glomerular filtration (inhibition of vasodilator prostaglandins by the NSAIDs)). 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.
Ciclosporin:	The risk of a kidney-damaging effect due to ciclosporin is increased through the concomitant administration of certain nonsteroidal anti-inflammatory 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.
Potassium sparing diuretics:	The concomitant administration of Advil Cold & Flu Relief and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).
Corticosteroids:	Corticosteroids as these may increase the risk of adverse reactions, especially of the gastrointestinal tract (gastrointestinal ulceration or bleeding) (see section 4.4).
Phenytoin:	The concomitant use 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).
Probenecid and sulfinpyrazone:	Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.

Zidovudine:	Increased risk of haematological toxicity when NSAIDs are given with zidovudine.There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
Sulfonylureas:	Clinical investigations have shown interactions between nonsteroidal anti-inflammatory drugs and antidiabetics (sulfonylureas). Although interactions between ibuprofen and sulfonylureas 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;Ginkgo biloba:	Increased risk of bleeding.
Cardiac Glycosides (e.g. Digoxin):	NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels. Serum digitalis concentrations should therefore be monitored in patients with decreased renal function or congestive heart failure.
Mifepristone:	NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
Antacids**:**	Certain antacids may increase the gastrointestinal absorption of Ibuprofen. This is considered to be of clinical relevance particularly during long-term use of Ibuprofen.
Aminoglycosides:	Reduction in renal function in susceptible individuals decreased elimination of aminoglycosides and increased plasma concentrations.

4.6 Fertility, pregnancy and lactation

Advil Cold & Flu Relief is contraindicated during pregnancy and breastfeeding (see section 4.3).

Pregnancy

Pseudoephedrine
There is a possible association between the development of fetal abnormalities and first trimester exposure to pseudoephedrine. Therefore the use of pseudoephedrine during pregnancy should be avoided.

Ibuprofen
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 gastroschisis 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.

From the 20th week of pregnancy onward, Advil Cold & Flu Relief use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/ closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above) 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.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy (see section 4.3).
Breast-feeding

Ibuprofen
In limited studies, ibuprofen appears in the breast milk in very low concentrations and is unlikely to affect the breast-fed infant adversely.

Pseudoephedrine
Pseudoephedrine is excreted in breast milk in small quantities, but the effect of this on breast-fed infants is not known.
It is estimated that 0.4% to 0.7% of a single dose of pseudoephedrine ingested by the mother will be excreted in breast milk over 24 hours.

In summary, the use of this product is contraindicated during pregnancy and breast-feeding (see section 4.3).

Fertility
There is limited evidence that drugs which inhibit cyclo-oxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

4.7 Effects on ability to drive and use machines

Advil Cold & Flu Relief has no or negligible influence on the ability to drive and use machines. Patients who experience dizziness, hallucinations, unusual headaches and visual or hearing disturbances should avoid driving or using machinery. Single administration or short-term use of this medicine does not usually warrant the adoption of any special precautions.

4.8 Undesirable effects

The most common observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, abdominal distension, mouth ulcerations, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed

Hypersensitivity reactions have been reported following treatment with Ibuprofen. These may consist of;
a) non-specific allergic reaction and anaphylaxis,
b) **Breathing:** respiratory tract reactivity comprising of asthma, aggravated asthma, bronchospasm or dyspnoea,
Skin: assorted skin disorders, including rashes of various types, bruising pruritis, urticaria, purpura, angiodema and more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).
c) Very rarely, bullous reactions including Steven's – Johnson syndrome and toxic epidermal necrolysis.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4). Oedema, hypertension, angina pectoris and cardiac failure have been reported in association with NSAID treatment.

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 Advil Cold & Flu Relief immediately and consult a doctor if they experience a serious adverse drug reaction.

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 (e.g. anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis)
Immune system disorders	Ibuprofen	Uncommon	Hypersensitivity reactions with urticaria, pruritus 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, tachycardia, drop in blood pressure, anaphylactic shock
Psychiatric disorders	Ibuprofen	Very rare	Psychotic reactions, depression, nervousness.
	Pseudoephedrine hydrochloride	Not known	Agitation, hallucination, anxiety, abnormal behaviour, insomnia, excitability, irritability, nervousness, restlessness
Nervous system disorders	Ibuprofen	Uncommon	Central nervous system disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness
	Ibuprofen	Not Known	Cerebrovascular accident (stroke)
	Pseudoephedrine hydrochloride	Not known	Haemorhagic stroke, ischemic stroke, convulsion, headache,insomnia, nervousness, anxiety, agitation, tremor, hallucinations, dizziness, psychomotor hyperactivity.
Eye disorders	Ibuprofen	Uncommon	Visual disturbances
	Pseudoephedrine hydrochloride	Not known	Ischaemic optic neuropathy
Ear and labyrinth disorders	Ibuprofen	Rare	Tinnitus
	Ibuprofen	Not known	Vertigo
Cardiac disorders	Ibuprofen	Very rare	Palpitations, heart failure, myocardial infarction, oedema, hypertention
	Pseudoephedrine hydrochloride	Not known	Palpitations, tachycardia, chest pain, arrythmia
Vascular disorders	Ibuprofen	Very rare	Arterial hypertension
	Pseudoephedrine hydrochloride	Not known	Hypertension
Respiratory, thoracic and	Pseudoephedrine hydrochloride	Rare	Exacerbation of asthma or hypersensitivity reaction with bronchospasm

mediastinal disorders			
Gastrointestinal disorders	Ibuprofen	Common	Dyspepsia, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation, anorexia, minor gastrointestinal blood loss in rare cases leading to anaemia
	Ibuprofen	Uncommon	Gastric ulcer with bleeding and/or perforation, 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, ischaemiccolitis
Hepatobiliary disorders	Ibuprofen	Very rare	Hepatic dysfunction, hepatic damage, particularly in long-term therapy, hepatic failure, acute hepatitis, jaundice
Skin and subcutaneous tissue disorders	Ibuprofen	Uncommon	Various skin rashes
	Ibuprofen	Very rare	Bullous exanthema such as Stevens-Johnson syndrome, and toxic epidermal necrolysis (Lyell syndrome), alopecia, severe skin infections, soft-tissue complications in a varicella infection
	Ibuprofen	Not known	Angioedema, erythema multiforme, skin eruption, rash, purpura, pruritus, urticaria. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Photosensitivity reactions.
	Pseudoephedrine hydrochloride	Not known	Rash, urticaria, pruritus, hyperhidrosis.
	Ibuprofen and Pseudoephedrine hydrochloride	Not known	Severe skin reactions, including acute generalized exanthematous pustulosis (AGEP)
Renal and Urinary disorders	Ibuprofen	Rare	Kidney-tissue damage (papillary necrosis) and elevated uric acid concentrations in the blood
	Ibuprofen	Very rare	Oedemas (particularly in patients with arterial hypertension or renal insufficiency), nephrotic syndrome, interstitial nephritis, acute renal insufficiency
	Ibuprofen	Not known	Hematuria, renal failure, proteinuria, oliguria
	Pseudoephedrine hydrochloride	Not known	Difficulty in micturition (Urinary retention in men with urethra-prostatic disorders.)
Investigations	Ibuprofen	Not Known	Haematocrit decreased and haemoglobin decreased
General disorders and administration site conditions	Ibuprofen	Not known	Oedema, swelling, peripheral oedema

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms
Over dosage may result in nervousness, agitation, anxiety, irritability, restlessness, dizziness, tremor, vertigo, insomnia, nausea, abdominal pain, vomiting, epigastric pain, diarrhoea, bradycardia, palpitation, tachycardia, tinnitus, headache, loss of consciousness, dyspnea, respiratory depression, seizures, illusions, hallucinations, behavioral disordersemydriasis, stroke and gastrointestinal bleeding. Hyperkalemia, hypertension or hypotension are also possible signs of overdose. Toxicity may manifest as drowsiness, excitation, disorientation or coma. The patient may develop convulsions. Hepatic function may be abnormal. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged. Acute renal failure and liver damage may occur. In asthmatics, exacerbationof asthma is possible.

Management
Due to the rapid absorption of the two active ingredients from the gastro-intestinal tract, emetics and gastric lavage must be instituted within four hours of overdosage to be effective. Charcoal is effective only if given within one hour.

Cardiac status should be monitored and the serum electrolytes measured.

If there are signs of cardiac toxicity, propranolol may be administered intravenously. A slow infusion of a dilute solution of potassium chloride should be initiated in the event of a drop in the serum potassium level. Despite hypokalaemia, the patient is unlikely to be potassium depleted, therefore overload must be avoided. Continued monitoring of the serum potassium is advisable for several hours after administration of the salt. For delirium or convulsions, intravenous administration of diazepam is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propionic acid derivatives, ibuprofen combinations
ATC code: M01AE51

Ibuprofen is a non steroidal anti-inflammatory agent belonging to the Propionic Acid class of drugs that has demonstrated its efficacy by inhibition of prostaglandin synthesis. It has analgesic, antipyretic and anti-inflammatory properties. Pseudoephedrine Hydrochloride is a sympathomimetic agent which causes vasoconstriction of nasal mucosa, thereby reducing rhinorrhoea and nasal congestion.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics studies show that when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys.

Absorption
Ibuprofen is rapidly absorbed from the gastrointestinal tract following administration. Maximum plasma concentrations occur about 1 to 2 hours after ingestion. Time for peak plasma concentrations to be reached may vary depending on dosage form and whether taken with food.

In an oral bioavailability study comparing solubilised ibuprofen (in the ibuprofen + pseudoephedrine soft capsules formulation) was shown to be bioequivalent to the ibuprofen plus pseudoephedrine tablet, and ibuprofen soft capsule for ibuprofen extent of exposure (AUC). The combination soft capsule formulation had greater peak exposure (Cmax) to ibuprofen than the tablet formulation. In addition, median time to peak exposure (Tmax) was comparable between ibuprofen + pseudoephedrine soft capsules (39 min) and comparator ibuprofen soft capsules (45 min), and was 20-30 minutes shorter than comparator ibuprofen + pseudoephedrine tablets (67.5 min).

The solubilized ibuprofen (as present in ibuprofen +pseudoephedrine soft capsules) displays a faster systemic absorption rate versus the comparator combination ibuprofen + pseudoephedrine tablet formulation.

Pseudoephedrine (in immediate release formulations) is readily absorbed from the gastrointestinal tract with peak plasma levels at 1-3 hours.

Distribution
Ibuprofen is primarily metabolized in the liver to primary metabolites 2-Hydroxyibuprofen and 2-Carboxyibuprofen. Ibuprofen is 90 to 99% bound to plasma proteins. In limited studies, Ibuprofen appears in the breast milk at very low concentrations.

Pseudoephedrine is thought to cross the placenta and to enter cerebrospinal fluid Pseudoephedrine distributes into breast milk; about 0.5% of an oral dose is distributed into breast milk over 24 hours.

Elimination
Ibuprofen has a plasma half-life of about 2 hours. It is rapidly excreted in the urine mainly as metabolites and their conjugates. About 1% is excreted in the urine as unchanged ibuprofen and about 14% as conjugated ibuprofen.

Pseudoephedrine is excreted largely unchanged in the urine with small amounts of its hepatic metabolite. It has a half-life of about 5 to 8 hours; elimination is enhanced and half-life accordingly shorter in acid urine. Small amounts are distributed into breast milk.

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

Liquid Fill:
Potassium hydroxide
Macrogol 600
Purified water

Gelatine Capsule:
Sorbitol liquid, partially dehydrated (E420)
Gelatine
Black printing ink (Macrogol 400, Polyvinyl Acetate Phthalate, Propylene Glycol, Iron Oxide Black (E172))

Processing aids:
Soya lecithin in Triglycerides, medium chain

6.2 Incompatibilities

No information is available.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Capsules are packed in to a white, opaque, PVC/PVdC heat sealed to Glassine/Aluminium foil blister strips,
or
white, opaque, PVC/PE/PVdC heat sealed to Glassine/Aluminium foil blister strips.
Blister strips packed in outer cardboard carton
Pack sizes: 2, 4, 8, 10, 12, 16, 20, 24
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Haleon Ireland Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0678/147/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th March 2016
Date of last renewal: 23rd December 2020

10 DATE OF REVISION OF THE TEXT

April 2023