SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sudafed Sinus Pressure & Pain 200mg/30mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg ibuprofen and 30 mg pseudoephedrine hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (Tablet).

Yellow, round, film-coated tablets. Diameter: approx. 11 mm, height: approx. 5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of nasal congestion associated with acute rhinosinusitis suspected to be of viral origin with headache and/or fever.

This product is indicated in adults and adolescents aged 15 years and older.

4.2 Posology and method of administration

Posology

Adults and adolescents aged 15 years and older:
1 tablet (equivalent to 200 mg ibuprofen and 30 mg pseudoephedrine hydrochloride) every 6 hours if necessary.
For more intense symptoms, 2 tablets (equivalent to 400 mg ibuprofen and 60 mg pseudoephedrine hydrochloride) every 6 hours if necessary, to a maximum total daily dose of 6 tablets (equivalent to 1200 mg ibuprofen and 180 mg pseudoephedrine hydrochloride).
The maximum total daily dose of 6 tablets (equivalent to 1200 mg ibuprofen and 180 mg pseudoephedrine hydrochloride) must not be exceeded.

For short-term use.

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

The patient should consult a doctor if symptoms worsen. The maximum duration of treatment is 4 days for adults and 3 days for adolescents aged 15 years and older.

In situations where the symptoms predominantly consist of either pain/fever or nasal congestion, administration of single entity products is to be preferred.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Paediatric population
This product is contraindicated in paediatric patients below 15 years of age (see section 4.3).

Method of administration
For oral use.
The tablets should be swallowed whole without chewing with a large glass of water, preferably during meals.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1;
- Patients aged under 15 years;
- Pregnant women during the third trimester of pregnancy (see section 4.6);
- Breast-feeding mothers (see section 4.6)
- Patients who have previously shown hypersensitivity reactions (e.g. bronchospasm, asthma, rhinitis, angioedema or urticaria) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs);
- History of gastrointestinal bleeding or perforation related to previous NSAIDs therapy;
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding);
- Cerebrovascular or other bleeding;
- Unexplained haematopoietic abnormalities;
- Severe hepatic insufficiency;
- Severe acute or chronic kidney disease/ renal failure;
- Severe heart failure (NYHA Class IV);
- Severe cardiovascular disorders, coronary heart disease (heart disease, hypertension, angina pectoris), tachycardia, hyperthyroidism, diabetes, pheochromocytoma;
- 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;
- Systemic 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 non-selective monoamine oxidase inhibitors (MAOIs) (iproniazid) (see section 4.5) or use of monoamine oxidase inhibitors within the last two weeks.

4.4 Special warnings and precautions for use

Concomitant use of this product with other NSAIDs including cyclo-oxygenase (COX)-2 selective 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).

If symptoms persist beyond the recommended maximum duration of treatment with this medicinal product (4 days for adults and 3 days for adolescents), measures to be taken should be re-evaluated, in particular the possible usefulness of an antibiotic treatment.

Acute rhinosinusitis, suspected to be of viral origin, is defined by moderate intensity, bilateral rhinological symptoms dominated by nasal congestion with serous or puriform rhinorrhea, occurring in an epidemic context. The puriform appearance of rhinorrhea is common and does not systematically correspond to bacterial superinfection.

Sinus pains, during the first days of the illness, are associated with congestion of the sinus mucosa (acute congestive rhinosinusitis) and most often are resolved spontaneously.

In the event of acute bacterial sinusitis, antiobiotic therapy is justified.

Special warnings related to pseudoephedrine hydrochloride:

- The dosage, the recommended maximum duration of treatment (4 days for adults and 3 days for adolescents) 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.
- Patients should not exceed the recommended dose and/or the recommended duration of treatment. Increased doses may ultimately produce toxicity. Continuous use can lead to tolerance resulting in an increased risk of overdosing. Depression may follow rapid withdrawal.

- Ischaemic colitis

  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.

- Ischaemic optic neuropathy

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

- Severe Skin reactions
  Severe skin reactions such as acute generalized 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 Sudafed Sinus Pressure & Pain 200mg/30mg film-coated tablets should be discontinued and appropriate measures taken if needed.Posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS)

  Cases of PRES and RCVS have been reported with the use of pseudoephedrine containing products (see section 4.8). The risk is increased in patients with severe or uncontrolled hypertension, or with severe acute or chronic kidney disease/renal failure (see section 4.3).

  Pseudoephedrine should be discontinued and immediate medical assistance sought if the following symptoms occur: sudden severe headache or thunderclap headache, nausea, vomiting, confusion, seizures and/or visual disturbances. Most reported cases of PRES and RCVS resolved following discontinuation and appropriate treatment.

-

Before using this medicinal 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).
- 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 this product 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 this product 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 this product 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.
- Due to the pseudoephedrine hydrochloride component the following conditions are contraindicated (see section 4.3): Severe cardiovascular disorders, coronary heart disease (heart disease, hypertension, angina pectoris), tachycardia, hyperthyroidism, diabetes, pheochromocytoma, history of stroke or presence of risk factors for stroke, history of myocardial infarction.

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).
- Ibuprofen may cause a severe allergic reaction, especially in patients allergic to acetylsalicylic acid. Symptoms may include hives, facial swelling, asthma (wheezing), shock, skin reddening, rash or blisters with or without pyrexia or erythema.
- 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 Sudafed Sinus Pressure & Pain 200mg/30mg film-coated tablets may precipitate an acute asthma attack, particularly in some patients who are allergic to acetylsalicylic acid or an NSAID (see section 4.3).
- Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to ibuprofen.

- 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 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 taking concomitant low-dose acetylsalicylic acid or other medicinal products likely to increase gastro-intestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, especially elderly patients, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly 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 Sudafed Sinus Pressure & Pain 200mg/30mg film-coated tablets should be discontinued immediately if gastro-intestinal bleeding or ulceration occurs. (see section 4.3)

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).

- 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. ≤ 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, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

  Cases of Kounis syndrome have been reported in patients treated with Sudafed Sinus Pressure & Pain 200mg/30mg film-coated tablets. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

- Before using this medicinal product, patients should consult their doctor in case of a blood clotting disorder.

- Medication overuse headache (MOH):

  Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

- 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.

- Severe cutaneous adverse reactions (SCARs):

  Severe cutaneous adverse reactions (SCARs) including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8). Most of these reactions occurred within the first month.

  If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately, and an alternative treatment considered (as appropriate).

- Masking of symptoms of underlying infections

  can mask symptoms of infection, which may lead to 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 to varicella. When Sudafed Sinus Pressure & Pain 200mg/30mg film-coated tablets is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospitals settings, the patient should consult a doctor if symptoms persist or worsen.

Precautions for use related to ibuprofen:

- Elderly: The pharmacokinetics of ibuprofen is not modified by age; no dose adjustment is necessary in the elderly. However, elderly patients should be carefully monitored as they have an increased frequency of 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. There is a risk of renal impairment in dehydrated adolescents.
- Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.
- If visual disturbances occur during the course of treatment, a full ophthalmological examination should be carried out.

Excipients

This medicine contains less than 1 mmol sodium (23mg) per tablet, that is to say "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Combination of pseudoephedrine with:	**Possible Reaction**

Non-selective MAOIs (iproniazid):	Paroxysmal hypertension and hyperthermia, which can be fatal. Because of the long duration of action of MAOIs, this interaction can occur up to 15 days after discontinuation of the MAOI.
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 hypertensive crises.
Volatile halogenated anaesthetics:	Perioperative acute hypertension. In scheduled surgery, discontinue treatment with this product several days before.
Guanethidine, reserpine and methyldopa:	Effect of pseudoephedrine may be diminished.
Tricyclic antidepressants:	Effect of pseudoephedrine may be diminished or enhanced.
Digitalis, chinidine or tricyclic antidepressants:	Increased frequency of arrhythmia.

Concomitant use of ibuprofen with :	**Possible Reaction**
Other NSAIDs, including salicylates and COX-2 selective inhibitors:	The concomitant administration of several 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 section 4.4).
Digoxin:	The concomitant use of this product with digoxin preparations may increase serum levels of these medicinal products. A check of serum-digoxin is not as a rule required on correct use (maximum over 4 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:	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: (e.g.: warfarin, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, iloprost)	NSAIDs as ibuprofen may enhance the effect of anti-coagulants (see section 4.4).
Phenytoin:	The concomitant use of this product 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 4 days).
Selective serotonin reuptake inhibitors (SSRIs):	Increased risk of gastrointestinal bleeding (see section 4.4).
Lithium:	The concomitant use of this product 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 4 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 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, 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 this product and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).
Methotrexate:	The administration of this product 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 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.
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

The use of this medicinal product is contra-indicated during the third trimester of pregnancy. During the first and second trimester it should only be given if clearly necessary and under supervision of a physician

Pseudoephedrine hydrochloride:

Studies in animals have shown reproductive toxicity (see section 5.3). The use of pseudoephedrine hydrochloride decreases maternal uterine blood flow but clinical data are insufficient with respect to effects on pregnancy.

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 prostaglandin synthesis inhibitors in early pregnancy. 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, ibuprofen 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. Therefore, during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used during the first

and second trimester of pregnancy, or by a woman attempting to conceive, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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, which may progress to renal failure with oligo-hydroamniosis (see above);

the mother and the child, 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, this medicine is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding

Measures which must be taken during lactation result from the presence of pseudoephedrine hydrochloride in the medicinal product formulation: pseudoephedrine hydrochloride is excreted in human breast milk. Considering the potential cardiovascular and neurological effects of vasoconstrictors, ingestion of this medicinal product is contra-indicated during lactation.

Fertility:

There is some 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

This product has minor or moderate 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 commonly-observed adverse reactions related to ibuprofen are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4 Special warnings and precautions for use) have been reported following

administration. Less frequently, gastritis has been observed. In general, the risk of development of adverse reactions (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 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).

The following list of adverse reactions 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 reactions may occur.

Patients should be informed that they should stop taking this product immediately and consult a doctor if they experience a serious adverse drug reaction.

<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 preexistent autoimmune diseases (Systemic Lupus Erythematosus (SLE), mixed connective tissue disease)
Blood and lymphatic system disorders	Ibuprofen	Very rare	Haematopoietic disorders (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
	Pseudoephedrine hydrochloride	Common	Insomnia
	Pseudoephedrine hydrochloride	Not known	Agitation, anxiety, hallucination, abnormal behaviour, euphoric mood, nervousness
Nervous system disorders	Ibuprofen	Uncommon	Central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness
	Pseudoephedrine hydrochloride	Rare	Restlessness, tremor,
	Pseudoephedrine hydrochloride	Not known	Headache, haemorhagic stroke, ischemic stroke, convulsion, somnolence
	Pseudoephedrine hydrochloride	Not known	Posterior Reversible Encephalopathy Syndrome(PRES) (see section 4.4), Reversible Cerebral Vasoconstriction Syndrome (RCVS) (see section 4.4)
Eye disorders	Ibuprofen	Uncommon	Visual disturbances

	Pseudoephedrine hydrochloride	Not known	Ischaemic optic neuropathy
Ear and labyrinth disorders	Ibuprofen	Rare	Tinnitus
Cardiac disorders	Ibuprofen	Very rare	Palpitations, heart failure, myocardial infarction
	Ibuprofen	Not known	Kounis syndrome
	Pseudoephedrine hydrochloride	Not known	Palpitations, tachycardia, chest pain, arythmia
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, constipation, minor gastrointestinal blood loss in rare cases leading to anaemia
	Ibuprofen	Uncommon	Gastrointestinal ulcers sometimes with bleeding and/or perforation, gastritis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4)
	Ibuprofen	Very rare	Oesophagitis, pancreatitis, intestinal diaphragm-like stricture
	Pseudoephedrine hydrochloride	Common	Dry mouth, nausea
	Pseudoephedrine hydrochloride	Not known	Thirst, vomiting, ischaemic colitis
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 cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome), Erythema multiforme, exfoliative dermatitis, alopecia, severe skin infections and soft-tissue complications in a varicella infection

	Ibuprofen	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalized exanthematous pustulosis (AGEP)
	Ibuprofen	Not known	Photosensitivity reactions
	Pseudoephedrine hydrochloride	Very Rare	Rash, pruritus
	Pseudoephedrine hydrochloride	Not known	Angioedema, severe skin reaction including acute generalized exanthematous pustulosis (AGEP), urticaria hyperhidrosis
Metabolism and Nutrition Disorders	Ibuprofen	Not known	Decreased Appetite Hypokalaemia*
Renal and Urinary disorders	Ibuprofen	Rare	Kidney-tissue damage (papillary necrosis) and elevated uric acid concentrations in the blood
	Ibuprofen	Very rare	Increase in serum creatinine, oedemas (particularly in patients with arterial hypertension or renal insufficiency), nephrotic syndrome, interstitial nephritis, acute renal insufficiency or failure
	Ibuprofen	Not known	Ureteric colic, dysuria Renal tubular acidosis*
	Pseudoephedrine hydrochloride	Not known	Difficulty in micturition Urinary retention, dysuria

*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The clinical effects of overdose are more likely to be due to the pseudoephedrine hydrochloride rather than ibuprofen in this medicinal product. The effects do not correlate well with the dose taken due to inter-individual sensitivity to sympathomimetic properties.

Overdosage may result in nausea and vomiting.

Symptoms of sympathomimetic effect

CNS depression: e.g. sedation, apnea, cyanosis, coma

CNS stimulation (which is more likely in children): e.g. insomnia, hallucinations, convulsions, tremor, mydriasis, anxiety, agitation.

Besides the symptoms already mentioned as undesirable effects, the following symptoms can occur: hypertensive crisis, cardiac arrhythmias, muscle weakness and tenseness, euphoria, excitement, thirst, chest pain, dizziness, tinnitus, ataxia, blurred vision, hypotension, rhabdomyolysis, hypokalemia, palpitations, hypertension, and ischaemic bowel infarction.

Ibuprofen-related symptoms (in addition to the gastro-intestinal and neurological symptoms already mentioned as undesirable effects)

Drowsiness, nystagmus; tinnitus, hypotension, loss of consciousness, abdominal pain, nausea, vomiting, lethargy, headache, renal failure, renal tubular acidosis, fulminant hepatic failure, bradycardia, tachycardia, atrial fibrillation.

Prolonged use at higher than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia.

In serious poisoning, metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur.

Therapeutic measures

No specific antidote is available.

Consider oral administration of activated charcoal if the patient presents within one hour of ingestion of a potentially toxic amount.
Electrolytes should be checked and ECG performed. In case of cardiovascular instability and/or symptomatic electrolyte imbalance, symptomatic treatment should be initiated.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cough and cold preparations; other cold preparations.
ATC code: R05X

Pseudoephedrine hydrochloride is a sympathomimetic agent which, when administered systemically, acts as a nasal decongestant.

Ibuprofen is an NSAID belonging to the propionic acid class of drugs. It is an arylcarboxylic acid derivative which has analgesic, antipyretic and anti-inflammatory properties as well as a short-acting inhibitory effect on platelet function. All of these properties are related to its ability to inhibit prostaglandin synthesis.

This product is a combination of a vasoconstrictor (pseudoephedrine hydrochloride) with an analgesic dose of an NSAID (ibuprofen).

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic 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:

At therapeutic doses, pharmacokinetics of ibuprofen is linear.

Absorption:

Peak serum levels are reached approximately 90 minutes after oral dosing.

With single oral dose administration, peak serum levels in adults, are proportional to the dose (C_{max} 17 ± 3.5 μg/ml for a 200 mg dose and 30.3 ± 4.7 μg/ml for a 400 mg dose). Absorption of ibuprofen is delayed by food ingestion.

Distribution:

Ibuprofen does not accumulate. It is 99% bound to plasma proteins.

In the synovial fluid, ibuprofen is recovered at steady concentrations two to eight hours after dosing, with C_{max} in the synovial fluid being about one third of plasma C_{max}. After administration of a 400 mg ibuprofen dose every 6 hours in breast-feeding

women, the amount of ibuprofen recovered in breast milk is less than 1 mg per 24 hours.

Biotransformation:

Ibuprofen does not have any enzyme-inducing effect. It is 90% metabolized and converted into inactive metabolites.

Elimination:

Ibuprofen is mainly excreted via the urine. Ibuprofen is completely excreted within 24 hours, with 10% eliminated unchanged and 90% in the form of inactive metabolites, mainly glucurono-conjugates.

Elimination half-life is approximately 2 hours.

The pharmacokinetic parameters of ibuprofen are only slightly modified in the elderly, in renal failure patients and in patients with hepatic insufficiency. The alterations observed do not require dosage adjustment.

Pseudoephedrine hydrochloride:

When administered by oral route, pseudoephedrine is excreted mainly via the kidney in unchanged form (70 to 90 %).

Elimination half-life depends on urinary pH.

Urine alcalinazation results in an enhanced increase in tubular reabsorption, and consequently the prolongation of the elimination half-life of pseudoephedrine.

5.3 Preclinical safety data

The LD_{50} values for the combination of ibuprofen and pseudoephedrine hydrochloride in acute oral toxicity studies were: 2.40 g/kg for mice and 1.45 g/kg for rats.

No repeated dose toxicity studies on the combination of ibuprofen and pseudoephedrine hydrochloride have been performed.

No mutagenicity was observed with ibuprofen and pseudoephedrine hydrochloride / ibuprofen in combination using the Ames test.

The subchronic and chronic toxicity of ibuprofen in animal experiments showed up mainly in the form of lesions and ulcerations in the gastro-intestinal tract. In studies in rats and mice, no evidence of carcinogenic effects of ibuprofen was found.

Reprotoxicity studies in mice and rats with individual ingredients (~ 100 mg/kg ibuprofen; ~15 mg/kg pseudoephedrine hydrochloride) nor a combination of these revealed no indication of maternal or foetal toxicity or teratogenicity.

At a maternally toxic dose, pseudoephedrine hydrochloride induced foetotoxicity (reduced foetal weight and delayed ossification) in rats. Fertility studies or peri-postnatal studies have not been performed for pseudoephedrine hydrochloride.

Published reproductive toxicity studies on ibuprofen demonstrated an inhibition of ovulation in rabbits and impaired implantation in different animal species (rabbit, rat, and mouse). Studies in rats and rabbits have demonstrated that ibuprofen passes the placenta; for maternally toxic doses, an increased incidence of malformations (e.g. ventricular septal defects) was observed.

The active substance ibuprofen may show an environmental risk for the aquatic environment, especially for fish.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Microcrystalline cellulose

Calcium hydrogen phosphate anhydrous

Croscarmellose sodium

Maize starch

Silica, colloidal anhydrous

Magnesium stearate

Tablet Coat

Hypromellose

Macrogol 400

Talc

Titanium dioxide (E171)

Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Child-resistant PVC/PVDC/aluminium foil blister.

Pack sizes: 10, 12, 20, 24 film-coated tablets

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

McNeil Products Limited
50 – 100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 15513/0396

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/06/2017

10 DATE OF REVISION OF THE TEXT

07/01/2025