Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Brufen 200 mg Effervescent Granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet contains 200 mg ibuprofen.

Each sachet contains 1111 mg sucrose and 66 mg sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent granules.
White granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the symptomatic relief of mild to moderate pain, such as headache, period pain, dental pain, and fever and pain in the common cold.

4.2 Posology and method of administration

For oral use and short-term use only.

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

The ibuprofen dose depends on the patient's age and body weight. The maximum single daily dose for adults and adolescents should not exceed 400mg of ibuprofen. More than 400mg at a time does not give a better analgesic effect.

The adult patient should consult a doctor if symptoms persist or worsen, or if Brufen Effervescent Granules is required for more than 3 days in case of fever and 5 days in case of pain.

Suitable for adults and children over 30 kg (over 8 years old).

Adults and adolescents ≥ 40 kg:
Initial dose, 200 mg or 400 mg ibuprofen. If necessary additional doses of 1 or 2 sachets (200 mg to 400 mg ibuprofen) can be taken.

Leave at least 4 hours between doses. A total dose of 1,200 mg ibuprofen should not be exceeded in any 24-hour period.

Body weight	**Single dose in number of sachets**	**Maximum daily dose in number of sachets**
≥40kg Adolescents, adults and the elderly	1 or 2 sachets (equivalent to 200 mg or 400 mg ibuprofen)	6 sachets (equivalent to 1,200 mg ibuprofen)

If in adolescents this medicinal product is required for more than 3 days or if symptoms worse, a doctor should be consulted.

Children ≥30 kg ***(over 8 years old)***:

Brufen Effervescent Granules should only to be used for children with at least 30 kg body weight. The maximum total daily dose of ibuprofen is 20 mg per kg of body weight, divided into 3 single doses with dosing intervals of 6 to 8 hours. The maximum recommended daily dose should not be exceeded. A total dose of 600 mg of ibuprofen should not be exceeded in any 24-hour period. For Ibuprofen Effervescent Granules for children the following dosing instruction applies:

Body weight	Single dose in number of sachets	Maximum daily dose in number of sachets
Children 30 kg – 39 kg (8-12 years)	1 (equivalent to 200 mg ibuprofen)	3 (equivalent to 600 mg ibuprofen)

If in children this product is required for more than 3 days or if the symptoms worsen the patient is advised to consult a doctor.

It is recommended that patients with sensitive stomachs take Brufen Effervescent Granules with food. If taken shortly after eating, the onset of action of Brufen Effervescent Granules may be delayed. If this happens do not take more Brufen Effervescent Granules than recommended within section 4.2 (posology) or until the correct re-dosing interval has passed.

Brufen 200 mg Effervescent Granules are not suitable for use in children under 8 years or weighing less than 30 kg.

Elderly
No special dose adjustment is required. Because of the possible undesirable effect profile (see section 4.4), it is recommended to monitor the elderly particularly carefully.

Renal impairment
No dose reduction is required in patients with mild to moderate impairment to renal function (patients with severe renal insufficiency, see section 4.3).

Hepatic impairment
No dose reduction is required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction, see section 4.3).

Method of administration
In order to achieve a faster onset of action, the dose may be taken on an empty stomach. It is recommended that patients with sensitive stomachs take ibuprofen with food.

The effervescent granules should be mixed with water to make an orange flavoured, fizzy drink. Empty the contents of the sachet into approximately 125 mL water, stir and drink as soon as effervescence subsides. The contents of the sachet cannot be divided between doses, and the entire contents of the sachet should be used. A transient sensation of burning in the mouth or throat may occur with Brufen Effervescent Granules; ensure that they are dissolved in plenty of water.

For oral administration.

4.3 Contraindications

Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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.

Ibuprofen should not be used in patients who have previously shown hypersensitivity reactions (e.g. bronchospasm, asthma, urticaria, angioedema or rhinitis) after taking ibuprofen, acetylsalicylic acid or other NSAIDs.

Severe hepatic failure.

Severe heart failure (NYHA Class IV) or coronary heart disease.

Severe renal failure (glomerular filtration below 30 mL/min).

Conditions involving an increased tendency to bleeding or active bleeding.

Severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

Dyshaematopoieis of unknown origin.

The third trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and gastrointestinal and cardiovascular effects below).
Caution is required in patients with certain conditions, which may be made worse:

- Systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis (see below and section 4.8).
- Gastrointestinal disorders and chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease) (see section 4.8).
- Renal impairment (see sections 4.3 and 4.8).
- Hepatic dysfunction (see sections 4.3 and 4.8).
- Directly after major surgery.
- Disturbed haematopoiesis
- Blood coagulation defects
- In patients with hypertension and/or cardiac impairment, as renal function may deteriorate (see sections 4.3 and 4.8).
- In patients who have had hypersensitivity or allergic reactions, as they could be at an increased risk of hypersensitivity reactions occurring with Brufen Effervescent Granules.
- In patients who suffer from hayfever, nasal polyps or chronic obstructive respiratory disorders, as there is an increased risk of allergic reactions occurring in these patients. These may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria.

There is some evidence that drugs which inhibit cyclooxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

The use of ibuprofen with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the potential for additive effects (see section 4.5).

Elderly
Elderly patients have an increased frequency of adverse reactions toNSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal.

Cardiovascular effects
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2,400 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. ≤ 1,200 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 (2,400 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 (2,400 mg/day) are required.

Gastrointestinal bleeding, ulceration and perforation
Gastrointestinal 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 gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses in patients with a history of ulcer, especially if complicated with bleeding or perforation (see section 4.3), and in the elderly. These patients should commence treatment at the lowest dose available. Combination therapy with protective drugs (e.g. misoprostol or proton pump inhibitors) should be considered for these patients as well as for patients requiring concomitant low dose acetylsalicylic acid, or other medicinal products likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, particularly elderly patients, should be told to report any unusual abdominal symptoms (especially gastrointestinal bleeding), particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medication which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin re-uptake inhibitors or antiplatelet drugs such as acetylsalicylic acid (see section 4.5).

Treatment with ibuprofen should be withdrawn if the patient suffers from gastrointestinal bleeding or ulceration.

NSAIDs should be given with care to patients with a history of gastrointestinal disease e.g. ulcerative colitis and Crohn's disease as these conditions may be exacerbated (see section 4.8).

Renal effects
Ibuprofen may cause the retention of sodium, potassium and fluid in patients who have not previously suffered from renal disorders because of its effect on renal perfusion. This may cause oedema or even lead to cardiac insufficiency or hypertension in predisposed patients.

As with other NSAIDs, the prolonged administration of ibuprofen to animals has resulted in renal papillary necrosis and other pathological renal changes. In humans, there have been reports of acute interstitial nephritis with haematuria, proteinuria and occasionally nephrotic syndrome. Cases of renal toxicity have also been observed in patients in whom prostaglandins play a compensatory role in the maintenance of renal perfusion. In these patients, administration of NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of suffering this reaction are those with renal dysfunction, heart failure, hepatic dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID treatment is generally followed by recovery to the pre-treatment state.

Caution should be exercised with regard to dehydrated patients particularly for children and the elderly. There is a risk of renal impairment in dehydrated children, adolescents and the elderly.

In general terms, the habitual intake of painkillers, particularly on combination of several pain-relieving active substances, may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore it should be avoided.

Respiratory disorders
Caution is required if ibuprofen is administered to patients suffering from, or with a previous history of, bronchial asthma, chronic rhinitis, sinusitis, nasal polyps, adenoids or allergic diseases since NSAIDs have been reported to precipitate bronchospasm, urticaria or angioedema in such patients.

Dermatological effects
Skin reactions
Severe skin reactions, some with a fatal outcome, such as exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in connection with the use of NSAIDs (see section 4.8). The risk of such reactions occurring is greatest at the start of the treatment, the majority of cases occurring during the first month. Acute generalized exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen – containing products. Treatment with ibuprofen should be withdrawn at the first signs of skin rash, mucosal damage or other signs of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues 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 Brufen Effervescent Granules in case of varicella.

Allergic reactions
Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed rarely. At the first signs of hypersensitivity reaction after taking/administering Brufen Effervescent Granules therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.
Caution is required in patients who have had hypersensitivity or allergic reactions to other substances, as they could be at an increased risk of hypersensitivity reactions occurring with Ibuprofen.

Masking of symptoms of underlying infections
Brufen 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 Brufen 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 precautions
Ibuprofen, the active substance of Brufen Effervescent Granules, may temporarily inhibit the blood-platelet function (thrombocyte aggregation) and prolong the bleeding time. Therefore, it is recommended to monitor patients with coagulation disturbances or on anticoagulant therapy carefully.

In prolonged administration of Brufen Effervescent Granules regular checking of the liver values, the kidney function, as well as of the blood count, is required.

During treatment with ibuprofen, some cases with symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed in patients with existing auto-immune disorders (such as Systemic Lupus Erythematosus, mixed connective tissue disease).

On prolonged use of painkillers, headache may occur that must not be treated with increased doses of the medicinal product.

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.

Information related to excipients
Brufen 200 mg Effervescent Granules contains 66 mg sodium per sachet. This is equivalent to 3.3% of the WHO recommended maximum daily dietary intake of 2g sodium for an adult.

Brufen 200 mg Effervescent Granules contains 1111 mg of sucrose per sachet. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose/galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

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

Concomitant use of ibuprofen with:	***Possible effects:***
Diuretics, ACE inhibitors, beta-blockers and angiotensin-II antagonists	NSAIDs may diminish the effect of these drugs. Diuretics and ACE-inhibitors can increase the risk of nephrotoxicity of NSAIDs. 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-blocker or angiotensin-II antagonist and agents that inhibit cyclooxygenase 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. The concomitant administration of ibuprofen and potassium sparing diuretics or ACE-inhibitors can result in hyperkalaemia. Careful monitoring of potassium levels is necessary.
Digoxin	NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma cardiac glycoside (e.g. digoxin) levels. The concomitant use of Brufen Effervescent Granules with digoxin preparations may increase serum levels of these medicinal products. A check of serum-digoxin should be considered if used over 4 days.
Lithium	The concomitant use of Brufen Effervescent Granules with lithium preparations may increase serum levels of these medicinal products. A check of serum-lithium should be considered if used over 4 days.
Methotrexate	NSAIDs inhibit the tubular secretion of methotrexate and certain metabolic interactions can occur resulting in decreased clearance of methotrexate. The administration of Brufen Effervescent Granules within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect. Therefore, concomitant use of NSAIDs and high doses of methotrexate should be avoided. Also, the potential risk of interactions in low dose treatment with methotrexate should be considered, especially in patients with impaired renal function. In combined treatment, renal function should be monitored.
Ciclosporin	The risk of a kidney-damaging effect due to ciclosporin is increased through the concomitant administration of certain non-steroidal anti-inflammatory drugs. This effect also cannot be ruled out for a combination of ciclosporin with ibuprofen.
Mifepristone	A decrease of the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid. Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.
Corticosteroids	Brufen Effervescent Granules should be used with caution in combination with corticosteroids as these may increase the risk of adverse reactions, especially of the gastrointestinal tract (gastrointestinal ulceration or bleeding) (see sections 4.3 and 4.4).
Anticoagulants	NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). In case of simultaneous treatment, monitoring of the coagulation state is recommended.
Acetylsalicylic acid	Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse events. 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 this 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).
Sulphonylureas	There are rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen. A check of blood glucose values is recommended as a precaution on concomitant use.
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. Blood counts 1-2 weeks after starting use together are recommended.
Other NSAIDs, including salicylates and cyclooxygenase-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).
Aminoglycosides	NSAIDs may decrease the excretion of aminoglycosides.
Cholestyramine	The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown. The medicinal products should be administered with at least 2 hours interval.
Tacrolimus	The risk of nephrotoxicity is increased if the two medicinal products are administered concomitantly.
Antiplatelet agents (e.g. clopidogrel and ticlopidine)	Increased risk of gastrointestinal bleeding (see section 4.4). NSAIDs should not be combined with ticlopidine due to a risk of an additive effect in the inhibition of the platelet function.
Selective serotonin reuptake inhibitors (SSRIs)	Increased risk of gastrointestinal bleeding (see section 4.4).
Herbal extracts	Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.
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.
CYP2C9 inhibitors	Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors) an increased S(+)-ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.
Phenytoin	The concomitant use of Ibuprofen Effervescent Granules 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).
Probenecid and sulfinpyrazone	Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.
Potassium-sparing diuretics	The concomitant administration of Ibuprofen Effervescent Granules and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).
Alcohol	The use of ibuprofen in individuals with chronic alcohol consumption (14-20 drinks/week or more) should be avoided due to increased risk of significant GI adverse effects, including bleeding.

4.6 Fertility, pregnancy and lactation

Fertility
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 an investigation of infertility, withdrawal of ibuprofen should be considered (see section 4.4).

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

During the first and second trimesters of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive or during the first and second trimester, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester, all prostaglandin synthesis inhibitors may expose:

The foetus to:
- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension),
- Renal dysfunction, which may progress to renal failure with oligohydramnios.

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

Consequently, ibuprofen is contraindicated during the last trimester of pregnancy.

Lactation
Ibuprofen is excreted in breast milk, but with therapeutic doses during short term treatment the risk for influence on infant seems unlikely. If, however, longer treatment is prescribed, early weaning should be considered.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery. This applies to a greater extent in combination with alcohol.

4.8 Undesirable effects

The most commonly observed adverse events 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) have been reported following administration. Less frequently, gastritis has been observed.

Undesirable effects are mostly dose-dependent. Especially the risk for the occurrence of gastrointestinal bleedings depends on the dosage range and duration of the treatment. Other known risk factors, see section 4.4.

Hypersensitivity:
Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, more rarely exfoliative and bullous dermatoses (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme).

Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of Brufen, the patient is recommended to go to a doctor without delay.

In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection.

Adverse events at least possibly related to ibuprofen are displayed by MedDRA frequency convention and system organ class. The following frequency groupings are used: 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) and Not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Uncommon	Rhinitis
	Rare	Meningitis aseptic
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.
Immune system disorders	Uncommon	Hypersensitivity reactions such as urticaria, pruritus, purpura and exanthema as well as asthma attacks (sometimes with hypotension)
	Rare	Severe hypersensitivity reactions Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock), Lupus erythematosus syndrome
Psychiatric disorders	Uncommon	Insomnia, anxiety
	Rare	Depression, confusional state, hallucinations
Nervous system disorders	Common	Headache, somnolence, dizziness, agitation,irritability
	Uncommon	Paraesthesia,
	Rare	Optic neuritis
Eye disorders	Uncommon	Visual impairment
	Rare	Toxic optic neuropathy
Ear and labyrinth disorders	Uncommon	Hearing impaired, tinnitus, vertigo
Cardiac disorders	Very rare	Cardiac failure, myocardial infarction (see section 4.4), palpitations,acute pulmonary oedema
Vascular disorders	Very rare	Hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	Asthma, bronchospasm, dyspnoea
Gastrointestinal disorders	Common	Dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melaena, haematemesis, gastrointestinal haemorrhage
	Uncommon	Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation
	Very rare	Pancreatitis, oesophagitis, intestinal strictures
	Not known	Exacerbation of Colitis and Crohn's disease
Hepatobiliary disorders	Uncommon	Hepatitis, jaundice, hepatic function abnormal
	Rare	Liver injury
	Very rare	Hepatic failure
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Urticaria, pruritus, purpura, angioedema, photosensitivity reaction

	Very rare	Bullous dermatoses, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme, exfoliative dermatitis, alopecia, necrotising fasciitis
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders	Uncommon	Tubulointerstitial nephritis, nephrotic syndrome and renal failure Acute renal failure, papillary necrosis (especially in long-term use) associated with increased serum urea
General disorders and administration site conditions	Common	Fatigue
	Rare	Oedema

Clinical studiessuggest that use of ibuprofen, particularly at a high dose (2,400 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 and heart failure as well as deterioration of ulcerative colitis and Crohn's disease have been reported in connection with NSAID treatment.

A transient sensation of burning in the mouth or throat may occur with Brufen Effervescent Granules.

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, Website: www.hpra.ie

4.9 Overdose

Toxicity
Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults. However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400 mg/kg or greater.

Symptoms
Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours.

The most frequently reported symptoms of overdose include nausea, vomiting, abdominal pain, lethargy and drowsiness. Central nervous system (CNS) effects include headache, tinnitus, dizziness, convulsion and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnea and depression of the CNS and respiratory system have also been rarely reported. Cardiovascular toxicity, including hypotension, bradycardia and tachycardia, has been reported. In cases of significant overdose, renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other drugs are being taken.

Treatment
There is no specific antidote for ibuprofen overdose. Gastric emptying followed by supportive measures is recommended if the quantity ingested exceeds 400 mg/kg within the previous hour.

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life threatening overdose.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

For the most current information, contact the local poison control centre.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: Anti-inflammatory and antirheumatic products, nonsteroids; propionic acid derivatives.
ATC code: M01AE01

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that in the conventional animal-experiment inflammation models has proven to be effective via prostaglandin-synthesis inhibition. In humans, ibuprofen reduces inflammatory-related pain, swellings and fever. Ibuprofen exerts an inhibitory effect on prostaglandin synthesis by inhibiting the activity of cyclo-oxygenase.

Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation.

Experimental data suggest that ibuprofen competitively may 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 (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of this data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicyclic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

Ibuprofen inhibits prostaglandin synthesis in the uterus, thereby reducing intrauterine rest and active pressure, the periodic uterine contractions and the amount of prostaglandins released into the circulation. These changes are assumed to explain the alleviation of menstrual pain. Ibuprofen inhibits renal prostaglandin synthesis which can lead to renal insufficiency, fluid retention and heart failure in risk patients (see section 4.3).
Prostaglandins are connected with ovulation and the use of medicinal products inhibiting prostaglandin synthesis may therefore affect the fertility of women (see sections 4.4, 4.6 and 5.3).

5.2 Pharmacokinetic properties

Absorption
On oral application, ibuprofen is partly absorbed in the stomach and then completely in the small intestine with a bioavailability of 80-90%. Peak plasma levels following oral administration occurred 1.7 hours (median value) after administration of the effervescent granules in the fasted state. If administered with food, peak serum concentrations were 34% lower and achieved approximately 2 hours later than when taken on an empty stomach. Food does not markedly affect total bioavailability.

Distribution
Ibuprofen is extensively bound to plasma proteins (99%). Ibuprofen has a small volume of distribution being about 0.12-0.2 L/kg in adults.

Metabolism
Ibuprofen is rapidly metabolized in the liver through cytochrome P450, preferentially CYP2C9, to two primary inactive metabolites, 2-hydroxyibuprofen and 3-carboxyibuprofen. Following oral ingestion of the drug, slightly less than 90% of an oral dose of ibuprofen can be accounted for in the urine as oxidative metabolites and their glucuronic conjugates. Very little ibuprofen is excreted unchanged in the urine.

Elimination
Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours. The excretion of ibuprofen is virtually complete 24 hours after the last dose.

Special populations
Elderly
Given that no renal impairment exists, there are only small, clinically insignificant differences in the pharmacokinetic profile and urinary excretion between young and elderly.

Children

The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5 mg/kg to 10 mg/kg body weight) in children aged 1 year or over, appears similar to that in adults.
Children 3 months to 2.5 years appeared to have a higher volume of distribution (L/kg) and clearance (L/kg/h) of ibuprofen than did children >2.5 to 12 years of age.

Renal impairment
For patients with mild renal impairment increased unbound (S)-ibuprofen, higher AUC values for (S)-ibuprofen and increased enantiomeric AUC (S/R) ratios as compared with healthy controls have been reported.

In end-stage renal disease patients receiving dialysis the mean free fraction of ibuprofen was about 3% compared with about1% in healthy volunteers. Severe impairment of renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis (see sections 4.2, 4.3 and 4.4).

Hepatic impairment
Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters.

In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) treated with racemic ibuprofen an average 2-fold prolongation of the half-life was observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of (R)-ibuprofen to the active (S)-enantiomer (see sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

The subchronic and chronic toxicity of ibuprofen in animal experiments was observed principally as lesions and ulcerations in the gastro-intestinal tract. In vitro and in vivo studies gave no clinically relevant evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found. Ibuprofen led to inhibition of ovulation in rabbits as well as disturbance of implantation in various animal species (rabbit, rat, mouse).
Experimental studies have demonstrated that ibuprofen crosses the placenta, for maternally toxic doses, an increased incidence of malformations (e.g. ventricular septal defects) was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate, anhydrous
Croscarmellose sodium
Malic acid
Microcrystalline cellulose
Saccharin sodium
Sodium hydrogen carbonate
Sucrose
Povidone
Orange flavour
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

A heat-sealed sachet consisting of a paper/polyethylene/aluminium foil and polyethylene laminate.
Pack sizes: 12, 20 or 30 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
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Ireland

8 MARKETING AUTHORISATION NUMBER

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