Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Brufen 400 mg effervescent Granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet contains 400 mg ibuprofen.

Excipients with known effect
One sachet also contains 2222 mg sucrose and 131 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent granules.

White granules, with orange flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In adults and adolescents over 12 years (≥40 kg)
- Acute mild to moderate pain, such as headache and dental pain
- Primary dysmenorrhoea.
- Fever

4.2 Posology and method of administration

Posology
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 400 mg of ibuprofen.

Adults and adolescents older than 12 years (≥40 kg)
400 mg given as a single dose or up to 3 times a day with an interval of 4 to 6 hours.
More than 400 mg at a time does not give a better analgesic effect.

The maximum daily dose should not exceed 1200 mg.

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

Adults
The patient should consult a doctor if symptoms worsen, or persist for more than 3 days in case of fever and 5 days in case of pain.

Paediatric population
Brufen400 mg effervescent Granules are not suitable for use in children under 12 years. Other more appropriate ibuprofen formulations are available for this population.

Elderly population
NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events (see sections 4.4 and 4.8). If treatment is considered necessary, the lowest dose for the shortest duration necessary to control symptoms should be used. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Impaired renal function
In patients with mild or moderate reduction of renal function, the dose should be kept as low as possible for the shortest duration necessary to control symptoms and renal function monitored. (For patients with severe renal failure see section 4.3).

Impaired liver function
In patients with mild or moderate reduction of liver function, the dose should be kept as low as possible for the shortest duration necessary. (For patients with severe liver failure 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 a glass of water, stir and drink immediately. 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; ensure that the granules are dissolved in plenty of water.

4.3 Contraindications

Brufen is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- previous hypersensitivity reactions (e.g. asthma, rhinitis, urticaria or angioedema) in response to acetylsalicylic acid or other NSAIDs
- history of gastrointestinal bleeding or perforation, related to previous NSAID therapy
- active, or history of, recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- severe hepatic or severe renal insufficiency
- severe heart failure (NYHA Class IV) or coronary heart disease
- last trimester of pregnancy (see section 4.6)
- significant dehydration (caused by vomiting, diarrhoea or insufficient fluid intake)
- cerebrovascular or other active bleeding
- dyshaematopoiesis of unknown origin
- children younger than 12 years of age.

4.4 Special warnings and precautions for use

The use of Brufen with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided.

Asthmatic patients are to seek their doctor's advice before using ibuprofen (see below).

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below). Higher than recommended doses may cause serious risks.

Brufen should only be administered under strict consideration of the benefit-risk ratio in the following conditions:
- Systemic Lupus Erythematosus (SLE) or other autoimmune diseases
- Congenital disturbance of porphyrin metabolism (e.g. acute intermittent porphyria)
- The first and second trimester of pregnancy
- Lactation

Special care has to be taken in the following cases:
- Gastrointestinal diseases including chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease)
- Cardiac insufficiency and hypertension
- Reduced renal function
- Hepatic dysfunction
- Disturbed haematopoiesis
- Blood coagulation defects
- Allergies, hay fever, chronic swelling of nasal mucosa, adenoids, chronic obstructive airway disease or bronchial asthma as an increased risk of allergic reactions occurring in these patients. These allergic reactions may present as asthma attacks (so-called analgesic asthma) Quincke's oedema or urticaria
- Immediately after major surgical interventions

Gastrointestinal bleeding, ulceration and perforation
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 medicinal products likely to increase gastrointestinal risk (see below and section 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 or heparin, 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 Brufen, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

Elderly population
The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

Cardiovascular and cerebrovascular 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, hypertension and oedema have been reported in association with NSAID therapy.

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.

Skin reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen –

containing products. Brufen must 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 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 in case of varicella.

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.

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.

There is a risk of renal impairment especially in dehydrated adolescents and the elderly.

Allergic reactions
Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed rarely. At the first signs of hypersensitivity reaction after taking/administering Brufen, 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 as they could be at an increased risk of hypersensitivity reactions occurring with Brufen.

Respiratory disorders
Bronchospasm, urticaria or angioedema may be precipitated in patients suffering from or with a previous history of bronchial asthma, chronic rhinitis, sinusitis, nasal polyps, adenoids or allergic diseases.

Other precautions

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.

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. This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore it should be avoided.

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).

Ibuprofen may temporarily inhibit platelet aggregation and prolong the bleeding time. Therefore, patients with coagulation defects or on anticoagulant therapy should be observed carefully.

In case of long-term treatment with ibuprofen, a periodical monitoring of hepatic and renal function as well as the blood count is necessary, especially in high risk patients.

Consumption of alcohol should be avoided since it may intensify side effects of NSAIDs, especially if affecting the gastrointestinal tract or the central nervous system.

Patients on ibuprofen should report to their doctor signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain or oedema.

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 on withdrawal of treatment (see section 4.6).

Information related to excipients
This product contains 2222 mg sucrose per dose. 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.

This medicinal product contains contains 131 mg sodium per sachet. This is equivalent to 6.6% of the WHO recommended maximum daily dietary intake of 2g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant use of ibuprofen with:	**Possible effects:**
Other NSAIDs including cyclooxygenase-2 selective inhibitors	As a result of synergistic effects, the concurrent use of several NSAIDs can increase the risk of gastrointestinal ulcers and haemorrhage. Co-administration of ibuprofen with other NSAIDs should therefore be avoided (see section 4.4).
Cardiac glycosides (Digoxin)	NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma levels of cardiac glycosides. Monitoring of serum digoxin is recommended.
Corticosteroids	Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
Anticoagulants	NSAIDs may enhance the effects of anticoagulants, such as warfarin or heparin (see section 4.4). In case of simultaneous treatment, monitoring of the coagulation state is recommended.
Antiplatelet-agents (e.g. clopidogrel and ticlopidine)	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 thesedata to the clinical situation and 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).
Selective serotonin reuptake inhibitors (SSRI)	Increased risk of gastrointestinal bleeding (see section 4.4).
Lithium	Co-administration of ibuprofen with lithium preparations can increase the serum level of these medicinal products. Checking the serum lithium level is necessary.
Ticlopidine	NSAIDs should not be combined with ticlopidine due to a risk of an additive effect in the inhibition of the platelet function.

Potassium sparing diuretics	Concomitant use may cause hyperkalaemia (check of serum potassium is recommended).
Captopril	Experimental studies indicate that ibuprofen counteracts the effect of captopril of increased sodium excretion.
Antihypertensive drugs (Diuretics, ACE inhibitors, angiotensin-II-antagonists)	Diuretics and ACE-inhibitors can increase the nephrotoxicity of NSAIDs. NSAIDs can reduce the effect of diuretics and antihypertensives, including ACE-inhibitors and beta-blockers. In patients with reduced kidney function (e.g. dehydrated patients or elderly patients with reduced kidney function), the concomitant use of an ACE inhibitor or angiotension II antagonist with a cyclooxygenase-inhibiting medicinal product can lead to further impairment of kidney function and through to acute renal failure. This is usually reversible. Such combinations should therefore only be used with caution, especially in elderly patients. The patients have to be instructed to drink sufficient liquid and periodic monitoring of the kidney values should be considered for the time immediately after the start of the combination therapy. The concomitant administration of ibuprofen and potassium-sparing diuretics or ACE-inhibitors can result in hyperkalaemia. Careful monitoring of potassium levels is necessary.
Methotrexate	NSAIDs inhibit the tubular secretion of methotrexate and certain metabolic interactions can occur resulting in decreased clearance of methotrexate. The administration of ibuprofen within 24 hours before or after the administration of methotrexate can lead to an elevated concentration of methotrexate and an increase in its toxic effects. 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 kidney damage by ciclosporin is increased by the concomitant administration of certain NSAIDs. This effect can not be ruled out for the combination of ciclosporin and ibuprofen either.
Tacrolimus	Elevated risk of nephrotoxicity.
Zidovudine	There is evidence of an increased risk of haemarthrosis and haematoma in HIV positive haemophilia patients receiving concurrent treatment with zidovudine and ibuprofen. There may be an increased risk of haematotoxicity during concomitant use of zidovudine and NSAIDs. Blood counts 1‑ 2 weeks after starting use together are recommended.
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 (e.g. voriconazole or fluconazole)	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.
Sulphonylureas	NSAIDs can increase the hypoglycemic effect of sulphonylureas. In the case of simultaneous treatment,

	monitoring of blood glucose levels is recommended.
Cholestyramine	Concomitant treatment with cholestyramine and ibuprofen results in prolonged and reduced (25%) absorption of ibuprofen. The medicinal products should be administered with at least two hours interval.
Aminoglycosides	NSAIDs can slow down the elimination of aminoglycosides and increase their toxicity.
Herbal extracts	*Ginkgo biloba* may potentiate the risk of bleeding with NSAIDs.
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.
Mifepristone	If NSAIDs are used within 8-12 days after mifepristone administration, they can reduce the effect of mifepristone.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 the 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 losses and embryo/foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimesters of pregnancy, Brufen should not be given unless clearly necessary. If Brufen is used by a woman attempting to conceive or during the first and second trimester, the dose should be kept as low as possible and duration of treatment as short as possible.

During the third trimester of pregnancy, 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:
- 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, Brufen is contraindicated during the last trimester of pregnancy.

Breast-feeding

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

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.

4.7 Effects on ability to drive and use machines

Ibuprofen generally has no adverse effects on the ability to drive and use machinery. However since at high dosage side effects such as fatigue, somnolence, vertigo (reported as common) and visual disturbances (reported as uncommon) may be experienced, the ability to drive a car or operate machinery may be impaired in individual cases. This effect is potentiated by simultaneous consumption of 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 stomatits, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

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

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.

- *Immune system disorders*

Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consists 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, very rarely erythema multiforme and bullous dermatoses (including Stevens-Johnson syndrome, toxic epidermal necrolysis).

- *Infections and infestations*

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 (see section 4.4).

- *Cardiac and vascular disorders*

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, and cardiac failure, have been reported in association with NSAID treatment.

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 (see section 4.4)
Blood and lymphatic system disorders	Rare	Leucopoenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia. The first symptoms or signs may include: 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. The symptoms may include: facial oedema, swelling of the tongue, internal laryngeal swelling with constriction of the airways, dyspnoea, tachycardia, fall of blood pressure to the point of life-threatening shock. Lupus erythematosus syndrome
Psychiatric	Uncommon	Anxiety

disorders	Rare	Depression, confusional state, hallucinations
Nervous system disorders	Common	Headache, somnolence, agitation, dizziness, insomnia, irritability
	Uncommon	Paraesthesia
	Rare	Optic neuritis
Eye disorders	Uncommon	Visual impairment
	Rare	Toxic optic neuropathy
Ear and labyrinth disorders	Common	Vertigo
	Uncommon	Hearing impaired
	Very rare	Tinnitus
Cardiac disorders	Very rare	Palpitations, heart failure, myocardial infarction, acute pulmonary oedema, 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, melena, haematemesis, gastrointestinal haemorrhage
	Uncommon	Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation
	Very rare	Oesophagitis, pancreatitis, 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

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

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely, diarrhoea. Tinnitus, headache, dizziness, vertigo and gastrointestinal bleeding may also occur. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. Children may also develop myoclonic cramps. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to the actions of circulating clotting factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Treatment

Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Gastric emptying or oral administration of activated charcoal is indicated if the patient presents

within one hour of the ingestion of more than 400 mg per kg of body weight. If the Brufen has already been absorbed, alkaline substances should be administered to promote the excretion of the acid ibuprofen in the urine. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Other measures may be indicated by the patient's clinical condition. Bronchodilators should be given for asthma. No specific antidote is available.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivatives. ATC code: M01AE01

Mechanism of action

Ibuprofen is a NSAID that possesses anti-inflammatory, analgesic and antipyretic activity. Animal models for pain and inflammation indicate that ibuprofen effectively inhibits the synthesis of prostaglandins. In humans, ibuprofen reduces pain possibly caused by inflammation or connected with it, swelling and fever. Ibuprofen exerts an inhibitory effect on prostaglandin synthesis by inhibiting the activity of cyclo-oxygenase. In addition, ibuprofen has an inhibitory effect on ADP (adenosine diphosphate) or collagen-stimulated platelet aggregation.

Pharmacodynamic effects

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).

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
Ibuprofen is rapidly absorbed from the gastrointestinal tract with a bioavailability of 80-90%. Peak serum concentrations occurred 1.7 hours (median value) after administration of ibuprofen 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.

Biotransformation
Ibuprofen is rapidly metabolised 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 bodyweight) 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 about 1% 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

As a well-established and widely used product, the pre-clinical safety of ibuprofen is well documented.

Ibuprofen's subchronic and chronic toxicity was mainly shown by animal tests as gastric tract damage and ulcers.

The *in vitro* and *in vivo* tests have not shown any clinically significant signs about ibuprofen's mutagenicity. Furthermore, no carcinogenic effects have been observed in mice and rats.

Ibuprofen inhibits ovulation in rabbits and impairs implantation in various animal species (rabbit, rat, and mouse). In reproduction tests undertaken with rats and rabbits, ibuprofen passed across the placenta. When using doses toxic to the mother, malformations occur more frequently (i.e. ventricular septum defects).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous sodium carbonate
Croscarmellose sodium
Malic acid
Microcrystalline cellulose
Sodium saccharin
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

Sachet consisting of a paper/polyethylene/aluminium foil and polyethylene laminate.

Pack sizes: 12, 15, 20, 30 or 40 sachets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

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

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited,
Unit 35/36,
Grange Parade,
Baldoyle Industrial Estate,
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2010/002/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 18th January 2013

Date of Last Renewal: 5th December 2017

10 DATE OF REVISION OF THE TEXT

February 2021