Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen 600 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg ibuprofen
Excipient with known effect: each tablet contains 70 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Ibuprofen 600 mg film-coated tablets: pink coloured, oblong shape, approximately 19 mm in length, 8 mm in width, biconvex, film coated tablets debossed with 'DL' separated by break line on one side and plain on other side. The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of pain and inflammation in rheumatoid arthritis (including systemic Juvenile Idiopathic Arthritis [sJIA]), osteoarthritis, seronegative arthropathies and in painful swelling and inflammation after soft tissue injuries.

4.2 Posology and method of administration

Posology

The treatment should start with the lowest dose anticipated to be effective, which can subsequently be adjusted, depending on the therapeutic response and any undesirable effects. In long-term treatment a low maintenance dose should be the aim.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).
Adults and adolescents (12 years and older, >40kg):
Rheumatic diseases
One 600 mg tablet three times daily. An interval of at least 4-6 hours should be allowed between doses. Some patients can be maintained on 600-1200mg daily. In severe or acute conditions, it can be advantageous to increase the dosage until the acute phase is brought under control, provided that the total daily dose does not exceed 2400mg in divided doses. This tablet cannot be halved and in some instances a different strength or formulation of ibuprofen must be used.

Juvenile Rheumatoid Arthritis
Adolescents over 12 years of age (>40 kg): The recommended dose is 20-30mg/kg body weight daily in 3 to 4 divided doses up to a maximum of 40 mg/kg body weight daily in severe cases. Ibuprofen 600mg tablet is not suitable for children and adolescents younger than 12 years of age as correct dosing is not possible.

Elderly
The elderly are at increased risk of serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy. If renal or hepatic function is impaired, dosage should be assessed individually.

Renal impairment
Caution should be taken with ibuprofen dosage in patients with renal impairment. The dosage should be assessed individually. The dose should be kept as low as possible and renal function should be monitored (see sections 4.3, 4.4 and 5.2).

Hepatic impairment

Caution should be taken with dosage in patients with hepatic impairment. The dosage should be assessed individually and the dose should be kept as low as possible (see sections 4.3, 4.4 and 5.2)

Method of administration

For oral use.

It is recommended that patients with sensitive stomachs take ibuprofen tablet with food. If taken shortly after eating, the onset of action of ibuprofen tablet may be delayed. To be taken preferably with or after food, with plenty of fluid. Ibuprofen tablets should be swallowed whole and not chewed, broken, crushed or sucked on to avoid oral discomfort and throat irritation.

4.3 Contraindications

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

Active gastric or duodenal ulcer or a history of recurrent gastrointestinal ulcer/bleeding (two or more clear episodes of demonstrable ulceration or bleeding).

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.

Gastrointestinal bleeding or perforation in connection with previous treatment with NSAIDs.

The third trimester of pregnancy (see section 4.6).

Because of cross-reactions, ibuprofen should not be given to patients who have developed hypersensitivity reactions, including symptoms of asthma, rhinitis or urticaria after taking acetylsalicylic acid or other NSAIDs.

In patients with cerebrovascular or other acute bleeding

Hematologic diseases (e.g. hemorrhagic diathesis, hematopoetic disorder)

In patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake),

Colitis ulcerosa

The 600 mg tablets are contraindicated in children aged less than 12 years.

4.4 Special warnings and precautions for use

General precautions
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).

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.

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

Cardiovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate 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 (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.

Caution is required when treating patients with a history of hypertension and/or heart failure, since fluid retention and oedema have been reported in connection with NSAID treatment.

Gastrointestinal bleeding, ulceration and perforation

There is a strong link between the dose and severe gastrointestinal bleeding. The concomitant administration of ibuprofen and other NSAIDs, including selective cyclooxygenase-2 (COX-2) inhibitors should be avoided.

Elderly patients are at greater risk of experiencing undesirable effects when treated with an NSAID, especially gastrointestinal bleeding and perforation, which may be fatal.

Potentially fatal gastrointestinal bleeding, ulceration and perforation have been reported in connection with treatment with all types of NSAID and have occurred at any time during treatment, with or without warning symptoms or previous episodes of severe gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher at increased doses of NSAIDs in patients with a history of ulcer, especially if complicated with bleeding or perforation (see section 4.3), and in the elderly. Patients with the above-mentioned risk factors should commence treatment at the lowest possible dose.

Treatment with mucosa-protective drugs (e.g. misoprostol or proton pump inhibitors) should be considered for these patients as well as for patients on low doses of a acetylsalicylic acid or other drugs that may increase the risk of undesirable gastrointestinal effects (see below and section 4.5).

Patients with a history of gastrointestinal reactions, particularly elderly patients, should be told to watch out for any unusual abdominal symptoms (especially gastrointestinal bleeding), particularly at the start of the treatment and, if such symptoms occur, to seek medical help.

Caution should be exercised 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

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

As with other NSAIDs, the long-term administration of ibuprofen has resulted in papillary necrosis and other pathological changes in the kidney. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of normal renal perfusion. In these patients the administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may cause kidney failure. Those who are at greatest risk of this are patients with renal impairment, heart failure, hepatic dysfunction, the elderly and patients on diuretics or ACE inhibitors. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Ibuprofen can cause fluid and sodium and potassium retention in patients who have never suffered from renal disorders due to its effects on renal perfusion. This can cause oedema or heart failure or hypertension in predisposed subjects.

In general, regular use of analgesics, especially combinations of various analgesic agents, has the potential to cause permanent renal damage including the risk of renal failure (analgesics nephropathy).

Haematological Effects
Ibuprofen can inhibit platelet aggregation, resulting in prolongation of bleeding time. Hence, careful monitoring of patients with coagulation disorders or taking anticoagulants is recommended.

Respiratory disorders
Caution is required if ibuprofen is administered to patients suffering from, or with a previous history of, bronchial asthma, chronic rhinitis or allergic disease since ibuprofen have been reported to cause bronchospasm, urticaria or angioedema in such patients.

Severe skin reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely in association with the use of NSAIDSs (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. Ibuprofen should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.
SLE and mixed connective tissue disease
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see below and section 4.8).

Aseptic meningitis
Aseptic meningitis has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Infections and infestations
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 ibuprofen in case of varicella.

Hypersensitivity reactions
Analgesics, antipyretics and non-steroidal anti-inflammatory drugs (NSAIDs) can cause potentially serious hypersensitivity reactions, including anaphylactic reactions, even in subjects with no previous exposure to this type of drug. The risk of hypersensitivity after ibuprofen intake appears to be higher in patients who have previously exhibited hypersensitivity to other analgesic agents, antipyretics, NSAIDs and in patients with bronchial hyper-responsiveness (asthma), hay fever, nasal polyps or chronic obstructive pulmonary disease or previous episodes of angioedema (see sections 4.3 and 4.8). The allergic reactions may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or hives.

Severe hypersensitivity reactions (e.g. anaphylactic shock) have been rarely reported. The treatment with ibuprofen should be immediately withdrawn at the first sign of hypersensitivity reaction.

Reduced cardiac, renal and hepatic function
In patients with renal, cardiac, or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function. This risk is further increased in patients taking combinations of different analgesic agents regularly. The lowest effective dose for the shortest period of time and periodic monitoring of clinical and laboratory parameters, especially in case of prolonged treatment, is recommended in patients with renal, cardiac, or hepatic impairment (see section 4.3).

Medication overuse headache
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.

Patients with gastrointestinal problems, SLE, haematological or coagulation disorders and asthma should be treated with care and be closely monitored during NSAID treatment, since their condition may be exacerbated by the NSAID.

Masking of symptoms of underlying infections
Ibuprofen Tablet 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 Ibuprofen Tablet 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.

Information related to excipients
Ibuprofen tablets contain lactose monohydrate and should not be given to patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

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

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with Ibuprofen should be avoided:

The dicumarol group: NSAIDs may increase the effect of anticoagulants such as warfarin Experimental studies show that ibuprofen reinforces the effects of warfarin on bleeding time. NSAIDs and the dicumarol group are metabolised by the same enzyme, CYP2C9.

Anti-platelet agents: NSAIDs should not be combined with antiplatelet agents such as ticlopidine due to the additive inhibition of the platelet function (see below).

Methotrexate: NSAIDs inhibit the tubular secretion of methotrexate and some metabolic interaction with reduced clearance of methotrexate may also occur as a result. Accordingly, in high-dose treatment with methotrexate one should always avoid prescribing NSAIDs (see below).

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).

Cardiac glycosides: NSAIDs can exacerbate heart failure, reduce glomerular filtration and increase plasma cardiac glycoside (e.g. digoxin) levels.

Mifepristone: A decrease in 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

Sulfonylureas: There are rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

Zidovudine: There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

The following combinations with Ibuprofen may require dose adjustment:

Antihypertensives: NSAIDs can reduce the effect of diuretics and other antihypertensive agents.
Diuretics can also increase the risk of nephrotoxicity of NSAIDs.

Aminoglycosides: NSAIDs may reduce the excretion of aminoglycosides. *Children:* Care should be taken during concomitant treatment with ibuprofen and aminoglycosides.

Lithium: Ibuprofen reduces the renal clearance of lithium, as a result of which serum lithium levels may rise. The combination should be avoided unless frequent checks of serum lithium can be carried out and a possible reduction in the dose of lithium made.

ACE inhibitors, angiotensin-II antagonists and diuretics:
There is an increased risk of acute renal failure, usually reversible, in patients with renal impairment (e.g. dehydrated and/or elderly patients) when treatment with ACE inhibitors or angiotensin-II antagonists is given at the same time as NSAIDs, including selective cyclooxygenase-2 inhibitors. The combination should, therefore, be given with care to patients with renal impairment, especially elderly patients. Patients should be adequately hydrated and a check of renal function should be considered after the initiation of combination treatment and at regular intervals during treatment (see section 4.4).

Beta-blockers: NSAIDs counteract the antihypertensive effect of beta-adrenoceptor blocking drugs.

Selective serotonin re-uptake inhibitors (SSRIs):
SSRIs and NSAIDs each entail an increased risk of bleeding, e.g. from the gastrointestinal tract. This risk is increased by combination therapy. The mechanism may possibly be linked to reduced uptake of serotonin in the platelets (see section 4.4).

Cyclosporine: The concomitant administration of NSAIDs and cyclosporine is thought to be capable of increasing the risk of nephrotoxicity due to decreased synthesis of prostacyclin in the kidney. Accordingly, in the event of combination treatment, renal function must be monitored closely.

Captopril: Experimental studies indicate that ibuprofen counteracts the effect of captopril on sodium excretion.

Colestyramine: The concomitant administration of ibuprofen and colestyramine retards and reduces (by 25%) the absorption of ibuprofen. These drugs should be given at an interval of at least 2 hours.

Thiazides, thiazide-related preparations and loop diuretics: NSAIDs can counteract the diuretic effect of furosemide and bumetanide, possibly through inhibition of prostaglandin synthesis. They can also counteract the antihypertensive effect of thiazides.

Tacrolimus: Concomitant administration of NSAIDs and tacrolimus is thought to be capable of increasing the risk of nephrotoxicity due to decreased synthesis of prostacyclin in the kidney. Accordingly, in the event of combination treatment, renal function should be monitored closely.

Methotrexate: The risk of a potential interaction between an NSAID and methotrexate should also be taken into account in connection with low-dose treatment with methotrexate, especially in patients with renal impairment. Whenever combination treatment is given, renal function should be monitored. Caution should be exercised if both an NSAID and methotrexate are given within 24 hours, as the plasma levels of methotrexate can increase, resulting in increased toxicity (see above).

Corticosteroids: Concomitant treatment gives rise to an increased risk of gastrointestinal ulceration or bleeding.

Antiplatelet drugs: Increased risk of gastrointestinal bleeding (see above).

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.

Other analgesics and cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs, including Cox-2 inhibitors, as this may increase the risk of adverse effects (see section 4.4).

Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

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.

Ritonavir: It is a possible increase in the concentration of NSAIDs.

Probenecid: It slows the excretion of NSAIDs, with possible increase of their plasma concentrations.

Pemetrexed: An interaction with pemetrexed as there is an increased risk of its toxicity by decreased renal clearance. In patients with an impaired renal function displaying a creatinine clearance between 45-80 ml/min, this combination is to be avoided. In patients with normal renal function, a precaution for use is sufficient based on laboratory tests of the renal function.

Interaction studies have only been performed on adults.

4.6 Fertility, pregnancy and lactation

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 gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk of 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 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, has also 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 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. 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, all prostaglandin synthesis inhibitors may expose the foetus to:
- Cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension),
- Renal dysfunction, (see above).

The mother and the neonate, at the end of pregnancy, to:
- Prolongation of bleeding time,
- Inhibition of uterine contractions, resulting in delayed or prolonged labour.

Consequently ibuprofen 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 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 investigation of infertility, withdrawal of ibuprofen should be considered.

4.7 Effects on ability to drive and use machines

Following treatment with ibuprofen, the reaction time of certain patients may be affected. This should be taken into account where increased vigilance is required. Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The undesirable effects are mainly associated with the pharmacological effect of ibuprofen on prostaglandin synthesis. The most common effects are dyspepsia and diarrhoea, which are estimated to occur in about 10–30% of treated patients.

Adverse events at least possibly related to ibuprofen are displayed by MedDRA frequency convention and system organ class database. The following frequency groupings are used: Very common (³1/10), Common (³1/100 to <1/10), Uncommon (³1/1000 to <1/100), Rare (³1/10000 to <1/1000), 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	Aseptic meningitis (see section 4.4)
Blood and lymphatic system disorders	Uncommon	Leukopenia, thrombocytopenia, agranulocytosis,
		aplastic anaemia and haemolytic anaemia
Immune system disorders	Uncommon	Hypersensitivity
	Rare	Anaphylactic reaction
Psychiatric disorders	Uncommon	Insomnia, anxiety
	Rare	Depression, confusional state
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Paraesthesia, somnolence
	Rare	Optic neuritis
Eye disorders	Uncommon	Visual impairment
	Rare	Toxic optic neuropathy
Ear and labyrinth disorders	Uncommon	Hearing impaired
	Rare	Tinnitus, vertigo
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
	Not known	Exacerbation of Colitis and Crohn's disease
Hepatobiliary disorders	Uncommon	Hepatitis, jaundice, abnormal hepatic function
	Rare	Liver injury
	Very rare	Hepatic failure
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Urticaria, pruritus, purpura, angioedema, photosensitivity reaction
	Very rare	Severe forms of skin reactions (e.g. erythema multiforme, bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis)
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) , Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders	Uncommon	Nephrotoxity in various forms e.g. tubulointerstitial nephritis, nephrotic syndrome and renal failure
General disorders and administration site conditions	Common	Fatigue
	Rare	Oedema
Cardiac disorders	Not known	Cardiac failure, myocardial infarction (also see section 4.4)
Vascular disorders	Not known	Hypertension

Cardiac disorders and vascular disorders:

Oedema, hypertension and heart 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 such as myocardial infarction or stroke (see section 4.4).

Gastrointestinal disorders:
The most commonly observed adverse events are gastrointestinal in nature. Nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, gastrointestinal hemorrhage and exacerbation of colitis and Crohn's disease (see section 4.3) have been reported following ibuprofen administration. Less frequently, gastritis, duodenal ulcer and gastric ulcer and gastrointestinal perforation have been observed. Gastrointestinal ulcers, perforation or bleeding may sometimes be fatal, especially in elderly persons (see section 4.4).

Immune system disorders:
Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reaction 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, bullous dermatoses (including Stevens- Johnson syndrome and toxic epidermal necrolysis).

Infections and infestations:
Rhinitis and aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).

If signs of an infection occur or get worse during use of Ibuprofen the patient is therefore recommended to go to a doctor without delay.

Skin and subcutaneous tissue disorders: In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations").
Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described.

Blood and lymphatic system disorders:
Ibuprofen can cause prolongation of bleeding time through reversible inhibition of platelet aggregation.

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
Risk of symptoms at doses >80–100 mg/kg. At doses >200 mg/kg there is a risk of severe symptoms, though with considerable variations between individuals. A dose of 560 mg/kg in a child aged 15 months gave severe intoxication, 3.2 g in a 6-year-old mild to moderate intoxication, 2.8–4 g in a 1½-year-old and 6 g in a 6-year-old severe intoxication even after gastric lavage, 8 g in an adult moderate intoxication and >20 g in an adult very severe intoxication. 8 g administered to a 16-year-old affected the kidney and 12 g in combination with alcohol administered to a teenager resulted in acute tubular necrosis.

Symptoms
Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours.
The predominant symptoms of overdose are ones from the gastrointestinal tract, e.g. nausea, abdominal pain and vomiting (possibly blood-streaked). Central nervous system effects include headache, tinnitus, confusion and nystagmus. At high doses loss of consciousness and convulsions (mainly in children) may occur. Cardiovascular toxicity, including bradycardia, tachycardia and hypotension have been reported. Hypernatraemia, kidney effects and haematuria may occur. In serious poisoning metabolic acidosis may occur. In significant overdose, renal failure and liver damage are possible. Hypothermia and ARDS have occasionally been reported.

Treatment
Management should be symptomatic and supportive 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.
In the event of gastrointestinal problems, administer antacids. In the event of hypotension, intravenous fluid and, if required, inotropic support. Ensure adequate diuresis. Correct acid-base and electrolyte disorders.
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, nonsteroids; propionic acid derivatives.
ATC code: M01AE01

Mechanism of action
Ibuprofen belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs). It contains the propionic acid derivative p-isobutyl-hydrothropic acid. Ibuprofen has anti-inflammatory, analgesic and antipyretic effects. The anti-phlogistic effect is comparable with that of acetylsalicylic acid and indometacin. The pharmacological effect of ibuprofen is probably associated with its ability to inhibit prostaglandin synthesis. Ibuprofen prolongs bleeding time through reversible inhibition of platelet aggregation.

Clinical efficacy and safety
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 ibuprofenmay 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 renal prostaglandin synthesis. In patients with normal renal function this effect is of no particular significance. In patients with chronic renal insufficiency, decompensated heart or liver insufficiency as well as conditions involving changes in plasma volume, the inhibited prostaglandin synthesis can lead to acute renal insufficiency, fluid retention and heart failure (see section 4.3).

5.2 Pharmacokinetic properties

Absorption
Ibuprofen is rapidly absorbed from the gastrointestinal tract with a bioavailability of 80-90%. Peak serum concentrations occur one to two hours after administration. If administered with food, peak serum concentrations are lower and achieved more slowly than when taken on an empty stomach Food does not affect markedly 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 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 (5mg/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

There are no preclinical data of relevance for the safety assessment, apart from what has already been taken into account in this summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Lactose monohydrate
Maize starch
Croscarmellose sodium
Colloidal anhydrous Silica
Microcrystalline cellulose
Magnesium stearate

Tablet Coating
Macrogol/PEG
TalcTitanium dioxide (E171)
Erythrosine aluminum lake (E127)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC - Aluminium blisters or PVC/PVdC – Aluminium Blisters
Pack sizes: 10, 14, 21, 28, 30, 40, 42, 50, 60, 84, 100 or 500 film-coated tablets in carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/165/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th October 2016
Date of last renewal: 4th July 2021

10 DATE OF REVISION OF THE TEXT

October 2023