Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen 400mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg ibuprofen.

Excipient with known effect: 26.66 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White or off-white, capsule-shaped film-coated tablets, marked I4 on one side. The tablets are approximately 17mm long and 8mm wide.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and adolescents from 12 years of age (≥40 kg)
Symptomatic treatment of pain and inflammation in arthritic diseases (e.g. rheumatoid arthritis), degenerative arthritic conditions (e.g. osteoarthritis), and in painful swelling and inflammation after soft tissue injuries.

Symptomatic treatment of:
- mild to moderate pain
- fever

4.2 Posology and method of administration

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

The duration of treatment is determined by the treating physician.
For rheumatic diseases, it may be necessary to take Ibuprofen 400mg film-coated tablets over a prolonged period of time.

Pain and/or fever
Adults and adolescents ≥ 40 kg body weight (from 12 years):
The initial dose is 200 mg or 400 mg ibuprofen.

If necessary, additional doses of 200 - 400 mg ibuprofen can be taken.
The dosing interval depends on the symptoms and the recommended maximum daily dose. It should not be less than 6 hours.
A total dose of 1200 mg ibuprofen should not be exceeded in a 24-hour period.

Other dosage forms or strengths may be more suitable for use.

Rheumatic diseases and painful swellings and inflammations after soft tissue injuries

Adults
The recommended single dose is 400 - 600 mg ibuprofen., and the recommended daily dose is 1200 – 1800 mg ibuprofen in divided doses. There should be at least 6 hours between doses.

For some patients, a maintenance dose of 600 - 1200 mg daily may be sufficient. In severe or acute conditions, it may be beneficial to increase the dose until the acute phase is brought under control, provided the total daily dose of 2400 mg is not exceeded.
The maximum single dose for adults should not exceed 800 mg.
Other dosage forms or strengths may be more suitable for use.

Adolescents from 12 years (≥ 40 kg body weight)
The recommended dose should be adjusted to body weight: 20 - 40 mg/kg daily divided into 3 - 4 single doses. A total daily dose of 2400 mg should not be exceeded.
Other dosage forms or strengths may be more suitable for use.

Paediatric population
Ibuprofen 400mg film-coated tablets are not suitable for use in adolescents and children under 12 years of age and is not suitable for adolescents weighing under 40 kg bodyweight.

Elderly
NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed (see section 4.4).
The patient should be regularly monitored for gastrointestinal bleeding during NSAID therapy. The dose should be adjusted individually for patients with impaired kidney or liver function.

Renal impairment:
In patients with impaired kidney function, caution is advised regarding the ibuprofen dose. The dose should be adjusted individually. The dose should be kept as low as possible, and kidney function should be monitored.
Ibuprofen is contraindicated in patients with severe kidney dysfunction (see section 4.3).

Hepatic impairment:
In patients with impaired liver function, caution is advised regarding the ibuprofen dose. The dose should be adjusted individually and kept as low as possible. Ibuprofen is contraindicated in patients with severe liver dysfunction (see section 4.3).

Method of administration
For oral use. It is recommended that patients with sensitive stomachs take ibuprofen with food. Take Ibuprofen tablets 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
- Ibuprofen should not be given to patients who have experienced asthma, urticarial or allergic-type reactions after taking acetylsalicylic acid/asprin or other NSAIDs.
- Severe heart failure (NYHA IV).
- Severe liver failure.
- Severe renal failure (glomerular filtration below 30mL/min).
- Conditions involving an increased tendency to bleed.
- Patients with cerebrovascular or other active bleeding.
- History of gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- Active, or history of recurrent peptic ulceration or gastrointestinal haemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding).
- During the third trimester of pregnancy (see section 4.6).
- Patients with unclarified blood-formation disturbances.
- Patients with severe dehydration (e.g. caused by vomiting, diarrhoea or insufficient fluid intake).

4.4 Special warnings and precautions for use

<u>General precautions</u>
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).

On prolonged use of any 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.

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.

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 (2400mg/ 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. ≤ 1200mg/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 (2400mg/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 (2400mg/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.

Cases of Kounis syndrome have been reported in patients treated with ibuprofen. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

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 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 aspirin (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 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, in the second place, 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. The symptoms are normally reversible following withdrawal of the NSAID.

For patients with renal, hepatic or cardiac impairment, use the lowest effective dose for the shortest possible duration and monitor renal function, especially in long-term treated patients (see also section 4.3).

Haematological effects
Ibuprofen can inhibit platelet aggregation, resulting in prolongation of bleeding time.

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 diseases since ibuprofen has been reported to cause bronchospasm, urticaria or angioedema in such patients.

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

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.

Masking of symptoms of underlying infections
Ibuprofen 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 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.

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.

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.

Excipients
Ibuprofen tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 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.

Sulphonylureas: There are rare reports of hypoglycaemia in patients on sulphonylurea 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.

Phenytoin: Concomitant use of ibuprofen with phenytoin preparations can increase the serum level of phenytoin. Monitoring of serum phenytoin levels is recommended.

The following combinations with ibuprofen may require dose adjustment:

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

NSAIDs may reduce the excretion of aminoglycosides.

Aminoglycosides: NSAIDs may reduce the elimination of 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).

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.

Quinolone antibiotics: Experimental data from animals indicate that NSAIDs may increase the risk of seizure associated with quinolone antibiotics. Patients concomitantly taking NSAIDs and quinolones may be at increased risk of developing seizures.

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 and 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, have 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 or second trimesters, 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, e.g. when driving a car. This applies to a greater extent in combination with alcohol.

4.8 Undesirable effects

The pattern of adverse events reported for ibuprofen is similar to that for other NSAIDs.

Gastrointestinal disorders:
The most commonly observed adverse events are gastrointestinal in nature. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, gastrointestinal haemorrhage and exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following ibuprofen administration. Less frequently, gastritis, duodenal ulcer, 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).

Skin and subcutaneous tissue disorders:
Exceptionally, occurrence of serious cutaneous and soft tissues infectious complications during varicella infection. Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described.

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 heart failure have been reported in connection with NSAID treatment.

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

Infections and infestations:
In the majority of cases where aseptic meningitis has been reported, there has been some form of underlying autoimmune disease (in particular, systemic lupus erythematosus and related connective tissue diseases).

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 (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 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	Meningitis aseptic (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, 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	Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, 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	Nephrotoxicity 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 (see section 4.4)
	Not known	Kounis syndrome
Vascular disorders	Not known	Hypertension

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the 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 8 g in an adult gave 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
The predominant symptoms are ones from the gastrointestinal tract, e.g. nausea, abdominal pains, vomiting (possibly blood-streaked), and headache, tinnitus, confusion and nystagmus. At high doses loss of consciousness, convulsions (mainly in children). Bradycardia, fall in blood pressure. Metabolic acidosis, hypernatraemia, kidney effects, haematuria. Possibly liver effects. Hypothermia and ARDS have occasionally been reported.

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

Treatment
If warranted, gastric lavage, carbon. In the event of gastrointestinal problems, antacids. In the event of hypotension intravenous fluid and if required inotropic support. Ensure adequate diuresis. Correction of acid-base and electrolyte disorders. Other symptomatic therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, nonsteroidal; 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 with the generic name ibuprofen. Ibuprofen has anti-inflammatory, analgesic and antipyretic effects. The anti-phlogistic effect is comparable with that of aspirin 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 400mg were taken within 8 hours before or within 30 minutes 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 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 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 two 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.

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

In animal trials, the subchronic and chronic toxicity of ibuprofen showed up mainly in form of lesions and ulcerations in the gastrointestinal tract.
In vitro and in vivo studies revealed 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 inhibited ovulation in rabbits and impaired implantation in various animal species (rabbit, rat, mouse). Experimental studies in rats and rabbits have shown that ibuprofen crosses the placenta. Following administration of maternotoxic doses, an increased incidence of malformations (ventricular septal defects) occurred in the progeny of rats.

Ibuprofen may pose a risk to the aquatic compartment (see section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Colloidal anhydrous silica
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Sodium laurilsulfate
Magnesium stearate

Tablet coating:
Hypromellose
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister pack comprising of trans PVC-Al Foil, enclosed in an outer carton containing: 12, 14, 15, 16, 20, 24, 28, 30, 48, 50, 56, 60, 84, 90, 100, 112, 250, or 500 film-coated tablets.

Not all pack sizes are marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3).

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

7 MARKETING AUTHORISATION HOLDER

Hualan Pharmaceuticals Limited
16/17 College Green
Dublin 2
Dublin
D02 V078
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23341/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT