Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen Rx Clonmel 400 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ibuprofen Rx Clonmel 400 mg
Each film-coated tablet contains 400 mg of ibuprofen.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Ibuprofen Rx Clonmel 400 mg: Oval (14 mm x 8 mm in diameter) white to off white film coated tablet debossed with 'I 6' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ibuprofen Rx Clonmel is indicated for 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 in adults and adolescents older than 12 years (≥ 40 kg).

Ibuprofen Rx Clonmel 400 mg is also indicated for symptomatic treatment of mild to moderate pain and fever in adults and adolescents older than 12 years (≥ 40 kg).

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.

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

Adults and adolescents older than 12 years (≥ 40 kg)

Rheumatic diseases and painful swelling and inflammation after soft tissue injuries
400 mg-800 mg three times daily. An interval of at least 4-6 hours should be allowed between doses. For more rapid relief of the morning stiffness, the first dose may be given on a fasting stomach. The dose should be reduced in the event of renal insufficiency.
The maximum dose in a 24-hour period is 2 400 mg.

Pain of mild to moderate intensity
200 mg-400 mg in a single dose or three to four times daily. An interval of at least 4-6 hours should be allowed between doses. Single doses exceeding 400 mg have not been shown to have any additional analgesic effect.
The maximum dose in a 24-hour period is 1 200 mg.

Fever
200 mg-400 mg one to three times daily as required. An interval of at least 4-6 hours should be allowed between doses.
The maximum dose in a 24-hour period is 1 200 mg.

Paediatric population

Children 6–12 years (> 20 kg)
Mild to moderate pain and fever
200 mg one to three times daily. An interval of at least 4-6 hours should be allowed between doses.
Maximum daily dose: 20 mg/kg body weight, but not more than 600 mg.

Tablets are not recommended for children under 6 years of age.

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
Tablets should be taken with a glass of water. Tablets should be swallowed whole and not chewed, broken, crushed or sucked on to avoid oral discomfort and throat irritation. It is recommended that patients with sensitive stomach take ibuprofen with food. If taken shortly after eating, the onset of action of ibuprofen may be delayed.

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

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).

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 (2 400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1 200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2 400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2 400 mg/day) are required.

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 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, 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 generalised 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.

Impaired female fertility
There is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment (see section 4.6).

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated 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.

<u>The following combinations with ibuprofen may require dose adjustment</u>
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. *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).

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.

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 trimester 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 of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and

ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

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, ibuprofen is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

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

Summary of the safety profile
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, melena, 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 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).

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 (2 400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke, see section 4.4).
Oedema, hypertension and heart failure 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).

Tabulated list of adverse reactions

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 (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data).

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.
Cardiac disorders	Not known	Cardiac failure, myocardial infarction (see section 4.4), Kounis syndrome.
Vascular disorders	Not known	Hypertension.
Respiratory, thoracic and mediastinal disorders	Uncommon	Asthma, bronchospasm, dyspnoea.
Gastrointestinal disorders	Common	Dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melaena, haematemesis, gastrointestinal haemorrhage.
	Uncommon	Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation.
	Very rare	Pancreatitis.
	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.

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
Symptoms of overdose usually appear 4 to 6 hours after ingestion. 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.

Management
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, non-steroids; 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-hydratropic acid with the generic name ibuprofen. 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 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 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

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
Cellulose, microcrystalline (E460)
Starch, pregelatinised (maize)
Povidone
Sodium laurilsulfate (E487)
Croscarmellose sodium (E468)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E572)

Film-coating

Titanium dioxide (E171)
Hypromellose (E464)
Hydroxypropyl Cellulose (E463)
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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/Alu blister pack in an outer carton box containing 10 or 12 tablets per blister or unit dose blister .

Pack sizes:
400 mg: PVC/Alu blisters containing 20, 30, 50, 100.
PVC/Alu perforated unit dose blisters 20x1, 30x1, 50x1, 100x1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/415/002

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