# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen Clonmel 200 mg film-coated tablets
Ibuprofen Clonmel Max Strength 400 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ibuprofen Clonmel 200 mg
Each film-coated tablet contains 200 mg of ibuprofen.

Ibuprofen Clonmel Max Strength 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 Clonmel 200 mg: Round (9 mm in diameter) white to off white film coated tablet debossed with 'G2' on one side.

Ibuprofen Clonmel Max Strength 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 Clonmel is indicated for the short-term symptomatic treatment of mild to moderate pain such as headache, dysmenorrhea (period pain), dental pain as well as fever and pain associated with the common cold.

Ibuprofen Clonmel is indicated in adults and adolescents with body weight from 40 kg (12 years of age and above).

### 4.2 Posology and method of administration

**Posology**
For short-term oral use only.

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

The ibuprofen dose depends on the patient's body weight and age.

Adults and adolescents with body weight from 40 kg (12 years of age and above)
The recommended dose is 200-400 mg given as a single dose or up to 3 times a day as required. The interval between doses should be at least 6 hours. The maximum daily dose should not exceed 1 200 mg in any 24-hour period.

If this medicinal product is required in adults for more than 3 days in fever and for more than 4 days in pain, or if the symptoms worsen, a doctor should be consulted.

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

Paediatric population
Ibuprofen Clonmel is not intended for adolescents weighing less than 40 kg or in children below 12 years of age.

***Special populations***
*Elderly*
The elderly are at increased risk of serious consequences of adverse reactions. If 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.

*Renal impairment*
Caution should be taken in patients with mild to moderate renal impairment. The dose should be kept as low as possible and renal function should be monitored (see section 4.4). The medicinal product is contraindicated in patients with severe renal failure (see section 4.3).

*Hepatic impairment*
Caution should be taken in patients with mild to moderate hepatic impairment. The dose should be kept as low as possible (see section 4.4). The medicinal product is contraindicated in patients with severe hepatic failure (see section 4.3).

Method of administration
For oral 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.
- History of hypersensitivity reactions (e.g. bronchospasm, asthma, urticaria, angioedema or rhinitis) associated with the intake of acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs (NSAIDs).
- History of gastrointestinal bleeding or perforation related to previous NSAID therapy.
- Active or history of recurrent peptic ulcer or gastrointestinal haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Severe heart failure (NYHA Class IV).
- Severe hepatic failure or severe renal failure.
- The third trimester of pregnancy (see section 4.6).

## 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 risks below).

The use of ibuprofen with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding (see section 4.5).

The concomitant consumption of alcohol with NSAIDs, including ibuprofen may increase the risk of adverse effects on the gastrointestinal tract, such as GI haemorrhage or the central nervous system, possibly due to an additive effect.

Caution is required in patients:
- with congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria)
- immediately after major surgery
- with dehydration
- who have had hypersensitivity or allergic reactions to other substances, as they could be at an increased risk of hypersensitivity reactions with Ibuprofen Clonmel
- who suffer from hay fever, nasal polyps or chronic obstructive respiratory disorders, as for them an increased risk of allergic reactions exists. These may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria.

Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of hypersensitivity reaction after taking Ibuprofen Clonmel, therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

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.

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.

Gastrointestinal bleeding, ulceration and perforation
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

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

Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

NSAIDs should be given with caution to patients with a history of ulcerative colitis or Crohn's disease as these conditions may be exacerbated (see section 4.8).

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

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

Clinical studies suggest that use of ibuprofen, particularly at a high dose (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.

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.

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

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).

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).

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*.

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).

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.

Other warnings
Ibuprofen can temporarily inhibit blood platelet function (thrombocyte aggregation). Patients with coagulation disturbances should therefore be carefully monitored.

During prolonged use of ibuprofen regular monitoring of liver function tests, renal function and blood counts is required.

Prolonged use of any type of analgesics for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

In general, habitual intake of analgesics, particularly a combination of several analgesic medicinal products, may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration.

Paediatric population
There is a risk of renal impairment in dehydrated children and adolescents.

Excipients
This medicinal product 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**

Antihypertensives (ACE inhibitors, beta-blockers and angiotensin II antagonists) and diuretics: NSAIDs may reduce the effect of anti-hypertensives, such as ACE inhibitors, angiotensin-II receptor antagonists, beta-blockers and diuretics. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, betareceptor-blocker or angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated, and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics can also increase the risk of nephrotoxicity of NSAIDs.

*Digoxin, phenytoin, lithium*
The concomitant use of Ibuprofen Clonmel with digoxin, phenytoin or lithium preparations may increase serum levels of these active substances. A check of serum-lithium, serum-digoxin

and serum-phenytoin levels is not as a rule required on correct use (maximum over 3 or 4 days).

*Cholestyramine*
The concomitant administration of ibuprofen and cholestyramine retards and reduces (by 25 %) the absorption of ibuprofen. These medicinal products should be given at an interval of at least 2 hours.

*Methotrexate*
The use of ibuprofen within 24 hours before or after use of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.

*Ciclosporin*
Increased risk of nephrotoxicity.

*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.

*Other NSAIDs including cyclooxygenase-2 selective inhibitors*
Concomitant use should be avoided as this may increase the risk of adverse effects (see section 4.4).

*Acetylsalicylic acid*
Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of 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 use (see section 5.1).

*Corticosteroids*
Increased risk of gastrointestinal ulceration or bleeding with NSAIDs (see section 4.4).

*Anticoagulants*
NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4).

*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.

*Sulfonylureas*
NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen. A check of blood glucose values is recommended as a precaution on concomitant intake.

*Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)*
Increased risk of gastrointestinal bleeding with NSAIDs (see section 4.4).

*Tacrolimus*
Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

*Zidovudine*
Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

*Aminoglycosides*
NSAIDs may decrease the excretion of aminoglycosides.

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

*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*
Concomitant use with ritonavir may result in increased plasma concentrations of NSAIDs.

*Alcohol, bisphosphonates and oxpentifylline (pentoxifylline)*
May potentiate the GI side effects and the risk of bleeding and ulceration.

*Baclofen*
Elevated baclofen toxicity.

*Potassium sparing diuretics*
The concomitant administration of ibuprofen and potassium-sparing diuretics may lead to hyperkalaemia.

*Probenecid and sulfinpyrazone*
Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.

**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 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
Only small amounts of ibuprofen and its metabolite pass into human breast milk. Since harmful effects to infants have not become known to date, interruption of breast-feeding is usually not necessary during short-term treatment with the recommended dose for fever and pain.

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. The use of ibuprofen 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

Ibuprofen generally has no or negligible influence on the ability to drive and use machines. However, since at higher dose central nervous undesirable effects such as tiredness and dizziness may occur, the ability to react and the ability to take part actively in road traffic and to operate machines may be impaired in individual cases. This applies to a greater extent in combination with alcohol.

## 4.8 Undesirable effects

Summary of the safety profile
The following list of adverse events relates to all adverse effects that were reported for ibuprofen, including those occurring in patients with high-dose, long-term treatment in rheumatism patients. The listed frequencies that are higher than very rare reports involve short-term use of daily doses of up to 1 200 mg ibuprofen for oral administration forms and up to 1 800 mg for suppositories.

The listed adverse events are predominantly dose-dependent and variable between patients.

*Gastrointestinal disorders*
The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following ibuprofen administration. Less frequently, gastritis has been observed.

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical studies suggest that use of ibuprofen, particularly at 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).

Tabulated list of adverse reactions
Frequency groupings are classified according to the subsequent conventions: 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*** | Very rare | Symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or clouding of consciousness on ibuprofen have been reported. Patients with autoimmune disorders (SLE, mixed connective tissue disease) appear to be predisposed. Necrotising fasciitis. |
| ***Blood and lymphatic system disorders*** | Very rare | Haematopoietic disorders (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial oral ulcerations, flu like symptoms, extreme fatigue, unexplained bleeding and bruising. |
| ***Immune system disorders*** | Uncommon | Hypersensitivity reactions with skin rash and itching, as well as asthma attacks (possibly with a drop in blood pressure). |
| | Very rare | Severe general hypersensitivity reactions. These may manifest as: swelling of the face, tongue and throat, dyspnoea, tachycardia, and drop in blood pressure up to a life-threatening shock. |
| ***Psychiatric disorders*** | Very rare | Depression, psychotic reactions. |
| ***Nervous system disorders*** | Uncommon | Headache, somnolence, vertigo, dizziness, insomnia, agitation, irritability or fatigue. |
| | Not known | Optic neuritis, paraesthesia. |
| ***Eye disorders*** | Uncommon | Visual impairment. |
| | Rare | Toxic optic neuropathy. |
| ***Ear and labyrinth disorders*** | Rare | Loss of hearing, tinnitus. |

| | | |
|---|---|---|
| ***Cardiac disorders*** | Very rare | Palpitations, heart failure, myocardial infarction. |
| | Not known | Kounis syndrome. |
| ***Vascular disorders*** | Very rare | Arterial hypertension, vasculitis. |
| ***Respiratory, thoracic and mediastinal disorders*** | Very rare | Asthma, bronchospasm, dyspnoea. |
| | Not known | Rhinitis. |
| ***Gastrointestinal disorders*** | Common | Gastrointestinal symptoms such as pyrosis, stomach ache, nausea, vomiting, flatulence, diarrhoea, constipation, and minor gastrointestinal bleeding, which may cause anaemia in exceptional cases. |
| | Uncommon | Gastrointestinal ulceration, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's Disease (see section 4.4), gastritis. |
| | Very rare | Pancreatitis, oesophagitis, formation of intestinal diaphragm-like strictures. |
| ***Hepatobiliary disorders*** | Very rare | Impaired liver function, liver failure, acute hepatitis, liver damage, particularly in case of prolonged treatment. |
| ***Skin and subcutaneous tissue disorders*** | Uncommon | Various skin rashes. |
| | Very rare | Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis), alopecia. |
| | Not known | Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)<br>Acute generalised exanthematous pustulosis (AGEP), photosensitivity reactions. |
| ***Renal and urinary disorders*** | Rare | Renal tissue damage (papillary necrosis), elevated uric acid blood concentrations, elevated urea concentration in the blood. |
| | Very rare | Oedema, particularly in patients with arterial hypertension or renal failure, nephrotic syndrome, interstitial nephritis which may be combined with acute renal failure. |

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 ADR Reporting, Website: https://medicinesauthority.gov.mt/adrportal.

## 4.9 Overdose

Symptoms

Symptoms of overdose may occur at a dose greater than 100 mg/kg. A dose greater than 400 mg/kg may cause severe overdose symptoms requiring medical intervention.
Symptoms of overdose usually appear 4 to 6 hours after ingestion.
Most patients who have ingested clinically important amounts of ibuprofen will develop no more than nausea, vomiting, abdominal pain, or more rarely diarrhoea. Nystagmus, blurred vision, tinnitus, headache and gastrointestinal bleeding may also occur. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as vertigo, dizziness, drowsiness, occasionally excitation and disorientation, loss of consciousness or coma. Occasionally patients develop convulsions.

Children may also develop myoclonic cramps.

In serious poisoning metabolic acidosis may occur.

Hypothermia and hyperkalaemia may also occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics. 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 is a non-steroidal anti-inflammatory drug (NSAID). In conventional animal experiments, it has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swelling and fever. Furthermore, ibuprofen reversibly inhibits 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 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).

### 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.

*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**

The subchronic and chronic toxicity of ibuprofen in animal trials showed up mainly in the form of lesions and ulcers in the gastrointestinal tract. *In vitro* and *in vivo* studies gave no clinically relevant evidence of the mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found.

Ibuprofen led to an inhibition of ovulation in rabbits and impaired implantation in various animal species (rabbit, rat, and mouse). Experimental studies in rats and rabbits have shown that ibuprofen crosses the placenta. Following the administration of maternotoxic doses, an increased incidence of malformations (ventricular septal defects) occurred in the offspring of rats.

Ibuprofen poses a risk to the aquatic environment (see section 6.6).

## 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)
Hydroxypropylcellulose (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 condition.

### 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:

200 mg: PVC/Alu blisters containing 10, 12, 20, 24, 30, 40, 48, 50, 100.
PVC/Alu perforated unit dose blisters containing 10x1, 12x1, 20x1, 24x1, 30x1, 40x1, 48x1, 50x1, 100x1 tablets.

400 mg: PVC/Alu blisters containing 10, 12, 20, 24, 30, 40, 50, 100.
PVC/Alu perforated unit dose blisters containing 10x1, 12x1, 20x1, 24x1, 30x1, 40x1, 50x1, 100x1 tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

MA1045/09501-2

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5th December 2025

## 10. DATE OF REVISION OF THE TEXT