

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Nurofen Long Lasting 300 mg prolonged-release tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg ibuprofen.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Prolonged release tablet.

White to off white capsule-shaped tablet, debossed with 'N12' on one side and plain on the other side.

Dimensions: 17.5 mm length, 7.5 mm width and 4.9 mm thickness

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Nurofen Long Lasting 300 mg Prolonged Release Tablets are indicated for the short-term treatment of mild to moderate pain expected to last longer than 6-8 hours, such as backache, muscular pain, joint pain, period pain, and dental pain.

Nurofen Long Lasting 300 mg Prolonged Release Tablets are indicated in adults only.

### 4.2 Posology and method of administration

*Adults (over 18 years of age) and the elderly:*

Initial dose is two tablets (2 x 300 mg ibuprofen). Then, if necessary, another dose of two tablets (2 x 300 mg ibuprofen) can be taken after 12 hours. The interval between doses should be at least 12 hours. Maximum daily dose is 1200 mg ibuprofen (4 tablets) which must not be exceeded in any 24-hour period.

For short term use only. The patient should consult a doctor if the symptoms persist or worsen or if the medicinal product is required for more than 4 days.

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

Special populations

Elderly:

No special dose adjustment is required. Because of the possible undesirable-effect profile (see section 4.4), the elderly should be monitored particularly carefully.

Renal impairment:

No dose reduction is required in patients with mild to moderate impairment to renal function (patients with severe renal insufficiency, see section 4.3).

Hepatic impairment:

No dose reduction is required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction, see section 4.3).

Paediatric population

Not indicated for use by children and adolescents under 18 years of age.

The safety and efficacy of this medicine in children and adolescents under 18 years old has not yet been established. No data are available.

Method of administration

The tablets should be swallowed whole, with a glass of water 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;
- Patients who have previously shown hypersensitivity reactions (e.g. bronchospasms, asthma, rhinitis, angioedema or urticaria) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs);
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding);
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy;
- Patients with cerebrovascular or other active bleeding;
- Patients with unclarified blood-formation disturbances;
- Patients with severe dehydration (e.g. caused by vomiting, diarrhoea or insufficient fluid intake);
- Patients with severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV) (see also section 4.4);
- During the last trimester of pregnancy (see section 4.6).

**4.4 Special warnings and precautions for use**

This Prolonged Release formulation is intended for situations where more than a single lower dose of treatment (Immediate Release formulation) is expected to be necessary.

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).

Caution is required in patients with certain conditions:

- systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis (section 4.8).
- Congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria)
- Renal impairment as renal function may deteriorate (see sections 4.3 and 4.8)
- Hepatic dysfunction (see sections 4.3 and 4.8)
- Patients with conditions involving an increased tendency to bleeding
- Directly after major surgery
- In patients who show allergic reactions to other substances, as they are also at a higher risk of hypersensitivity reactions when using Nurofen Long Lasting 300 mg Prolonged Release Tablets.
- In patients who suffer from hay fever, nasal polyps, chronic obstructive respiratory disorders, or have a history of allergic disease, as an increased risk exists for them of allergic reactions occurring. These may present as asthma attacks (so-called analgesics asthma), Quincke's oedema or urticaria.

Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of a hypersensitivity reaction after taking Nurofen Long Lasting 300 mg Prolonged Release Tablets therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Masking of symptoms of underlying infections

Nurofen Long Lasting 300 mg Prolonged Release Tablets 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 Nurofen Long Lasting 300 mg Prolonged Release Tablets are administered for pain relief in relation to infection, monitoring of infection is advised. In nonhospital 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.

### Kidneys:

Generally, habitual intake of painkillers, especially the combination of several painkillers, leads to permanent damage to the kidneys with the risk of kidney failure (analgesic nephropathy).

### Cardiovascular and cerebrovascular effects:

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

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g.  $\leq 1200$  mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

### Gastrointestinal (GI) effects:

The use of Nurofen Long Lasting 300 mg Prolonged Release Tablets with concomitant NSAIDs, including cyclo-oxygenase-2 selective inhibitors (COX-2) should be avoided (see section 4.5).

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

The elderly have an increased frequency of adverse reactions, particularly gastrointestinal bleeding and perforation, which can be fatal (see section 4.2).

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.

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

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

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low-dose acetylsalicylic acid, or other medicinal products likely to increase gastrointestinal risk (see below and section 4.5). Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

### Haematological effects

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

### Severe skin reactions:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (Lyell's syndrome), have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy, the onset of the reaction occurring in the

majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Nurofen Long Lasting 300 mg Prolonged Release Tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other signs of hypersensitivity.

Medication overuse headache:

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

Other notes:

In prolonged administration of Nurofen Long Lasting 300 mg Prolonged Release Tablets regular checking of the liver values, the kidney function, as well as of the blood count, is required.

*Impaired female fertility:* See section 4.6

Exceptionally, varicella can cause serious cutaneous and soft tissue infectious complications. Thus, it is advisable to avoid the use of ibuprofen in case of varicella.

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**

Ibuprofen should be avoided in combination with other NSAIDs including cyclooxygenase-2-selective inhibitors: simultaneous use of two or more NSAIDs should be avoided as this may increase the risk of side 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 ibuprofen use (see section 5.1).

#### **Ibuprofen should be used with caution in combination with:**

Aminoglycosides

NSAIDs may decrease the excretion of aminoglycosides.

Anticoagulants

NSAIDs may potentiate the effects of anticoagulants such as warfarin or heparin (see section 4.4).

Antihypertensive medicines (ACE inhibitors, beta-receptor blockers and angiotensin II antagonists) and diuretics

NSAIDs can reduce the effect of these medicinal products. In some patients with reduced kidney function (e.g. dehydrated patients or elderly patients with compromised kidney function), the concomitant administration of an ACE inhibitor, beta-receptor blocker or angiotensin II antagonists with a cyclooxygenase-inhibiting medicinal product can lead to further impairment of kidney function, and possibly acute renal failure, which is usually reversible.

Such combination should therefore only be used with caution, especially in elderly patients.

Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Diuretics may increase the risk of nephrotoxicity of NSAIDs.

Potassium-sparing diuretics

The concomitant administration of ibuprofen and potassium-sparing diuretics may cause hyperkalaemia (monitoring serum potassium levels is recommended).

#### Cholestyramine

At concomitant administration of ibuprofen and cholestyramine the absorption of ibuprofen is delayed and decreased (25%). The medicinal products should be administered with a few hours interval.

#### Corticosteroids

Increased risk of gastrointestinal ulceration and bleeding (see section 4.4).

#### Platelet aggregation inhibitors and selective serotonin reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding (see section 4.4).

#### 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 and fluconazole.

#### Digoxin, phenytoin, lithium

The concomitant use of <Product name to be completed nationally> with digoxin, phenytoin or lithium preparations may increase serum levels of these medicinal products. A check of serum-lithium, serum-digoxin and serum-phenytoin levels is not as a rule required on correct use (maximum over 4 days).

#### Methotrexate

There is evidence for a possible increase in plasma levels of methotrexate. The use of ibuprofen within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.

#### Ciclosporin

Increased risk of nephrotoxicity.

#### Mifepristone

If NSAIDs are used within 8-12 days after mifepristone administration they can reduce the effect of mifepristone.

#### Tacrolimus

Increased risk of nephrotoxicity if the two medicines are administered simultaneously.

#### Zidovudine

There is evidence of an increased risk of haemarthrosis and haematoma in HIV positive haemophilia patients receiving concurrent treatment with zidovudine and ibuprofen.

#### 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.

#### Sulfonylurea derivatives

Clinical studies have shown interactions between NSAIDs and anti-diabetic agents (sulphonylurea derivatives).

Monitoring of blood glucose levels is recommended in case of simultaneous use.

#### Probenecid and sulfinpyrazone

Medicines containing probenecid or sulfinpyrazone, can delay the excretion of ibuprofen.

#### Herbal extracts (Ginkgo biloba)

Ginkgo can increase the risk of bleeding with NSAIDs.

#### Alcohol

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.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy.

The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss 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 20<sup>th</sup> 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 (with 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.

### Lactation

Ibuprofen and its metabolites can be pass in very low concentrations (0.0008% of the initial dose) into the breast milk. No harmful effects to infants are known to date. Therefore, ibuprofen may be used during breast-feeding for short-term treatment of pain at the recommended dose.

### Fertility

There is some evidence that medicinal products which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

## 4.7 Effects on ability to drive and use machines

Nurofen Long Lasting 300 mg Prolonged Release Tablets has no or negligible influence on the ability to drive and use machines at recommended doses and duration of therapy. However, since at higher dosage central nervous system 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 isolated cases. This applies to a greater extent in combination with alcohol.

## 4.8 Undesirable effects

The list of the following undesirable effects comprises all undesirable effects that have become known under treatment with ibuprofen, also those under high-dose long-term therapy in rheumatism patients. The stated frequencies, which extend beyond very rare reports, refer to the short-term use of daily doses up to a maximum 1200mg ibuprofen for oral dosage forms and a maximum of 1800 mg for suppositories.

With the following adverse drug reactions, it must be accounted for that they are predominantly dose-dependent and vary interindividually.

The adverse events observed most often 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 administration. Less frequently, gastritis has been observed. Particularly the risk of gastrointestinal bleeding occurring is dependent on the dose range and the duration of use.

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

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Adverse events which have been associated with ibuprofen are given below, listed by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

<b>System Organ Class</b>	<b>Frequency</b>	<b>Adverse Event</b>
Infections and infestations	Very rare	<p>Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of nonsteroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the nonsteroidal anti-inflammatory drugs.</p> <p>If signs of an infection occur or get worse during use of Nurofen Long Lasting 300 mg Prolonged Release Tablets, the patient is therefore recommended to go to a doctor without delay. It is to be investigated whether there is an indication for an anti-infective/antibiotic therapy.</p> <p>The symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness clouding have been observed under ibuprofen. Patients with autoimmune disorders (SLE, mixed connective tissue disease) appear to be predisposed.</p>
Blood and Lymphatic System Disorders	Very rare	<p>Disturbances to blood formation (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis). The first signs may be fever, sore throat, superficial wounds in the mouth, influenza-like complaints, severe lassitude, nosebleeds and skin bleeding. In such cases the patient should be advised to discontinue the medicinal product immediately, to avoid any self-medication with analgesics or antipyretics and to consult a physician.</p> <p>The blood count should be checked regularly in long-term therapy.</p>
Immune System Disorders	Uncommon	Hypersensitivity reactions with urticaria and pruritus, as well as asthma attacks (possibly with drops in blood pressure).
	Very rare	Severe general hypersensitivity reactions. Symptoms could be; facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock). Exacerbation of asthma and bronchospasm.
	Unknown	Respiratory tract reactivity comprising asthma or dyspnoea

Psychiatric disorders	Very rare	Psychotic reactions, depression
Nervous System Disorders	Uncommon	Central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness
Eye disorders	Uncommon	Visual disturbances. In this case, the patient should be instructed to inform a physician immediately and stop using ibuprofen.
Ear and labyrinth disorders	Rare	Tinnitus, hearing impaired
Cardiac disorders	Very rare	Palpitations, heart failure, myocardial infarction
Vascular disorders	Very rare	Arterial hypertension, vasculitis
Gastrointestinal Disorders	Common	Gastro-intestinal complaints such as dyspepsia, pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation, and slight gastrointestinal blood losses that may cause anaemia in exceptional cases
	Uncommon	Gastrointestinal ulcers, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), gastritis
	Very rare	Oesophagitis, pancreatitis, formation of intestinal diaphragm-like strictures. The patient is to be instructed to withdraw the medicinal product and to go to a doctor immediately if severe pain in the upper abdomen or melaena or haematemesis occurs.
Hepatobiliary Disorders	Very rare	Hepatic dysfunction, hepatic damage, particularly in long-term therapy, hepatic failure, acute hepatitis
Skin and Subcutaneous Tissue Disorders	Uncommon	Various skin rashes
	Very rare	Bullous reactions including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis (Lyell's syndrome), alopecia. In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations").
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP), photosensitivity reactions
Renal and Urinary Disorders	Rare	Kidney-tissue damage (papillary necrosis) and elevated uric acid concentrations in the blood may also occur rarely. Elevated urea concentrations in the blood.
	Very rare	Formation of oedemas, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis that may be accompanied by acute renal insufficiency. Renal function should therefore be checked regularly.
Investigations	Rare	Decreased haemoglobin levels

### Description of selected adverse reactions

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm, dyspnoea or (c) assorted skin disorders, including rashes of various types pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

#### 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](http://www.hpra.ie).

### 4.9 Overdose



In children ingestion of more than 400mg/kg may cause symptoms. In adults the dose response effect is less clear cut.

#### *Symptoms:*

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/

INR may be prolonged, probably due to interference with the actions of circulating clotting factors.

Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

#### *Management:*

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

No special antidote is available.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: [Antiinflammatory and antirheumatic products, non-steroids](#), [Propionic acid derivatives](#)

ATC code: M01AE01

Mechanism of action and pharmacodynamic effects: Ibuprofen is a nonsteroidal anti-inflammatory Drug (NSAID) that in the conventional animal-experiment inflammation models has proven to be effective via prostaglandin-synthesis inhibition. In humans, ibuprofen reduces inflammatory-related pain, swellings and fever.

Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation.

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 (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).

In a randomised, double-blind, double-dummy, parallel-group, multiple-dose, active and placebo controlled dental pain study, the 300mg ibuprofen prolonged release (PR) group taking a single 2-tablet dose (2x300mg) demonstrated statistically significant and clinically meaningful pain relief compared to placebo from 30 minutes that was sustained consistently lasting up to 12 hours. The analgesic performance of PR (2 x 300mg) dosed at time zero and 12h was demonstrated to be comparable over a 24h period against that of IR (2 x 200mg) dosed at time zero, 8h and 16h.

In the intent-to-treat (ITT) population, the least squares (LS) mean standard error (SE) sum of pain intensity difference (SPID) 12-hour scores were statistically significantly higher in both the ibuprofen PR group and the ibuprofen IR group compared to the placebo group. The LS mean SPID24 scores were similar and the difference in LS means was not statistically significant when analysed in the ITT population.

The median (95% CI) time to meaningful pain relief was faster for the ibuprofen IR group (0.99 [0.84, 1.21] hours), followed by the ibuprofen PR group (1.25 [0.94, 1.54] hours) as compared to the placebo group (2.88 [1.98, not estimable] hours, P-value = 0.0075 and <0.0001 and for the ibuprofen PR and IR group, respectively).

After 24 hours, subjects were statistically significantly less likely to use rescue medication in the PR group (25%) and the IR group (16%) compared to those in the placebo group (82%).

### **5.2 Pharmacokinetic properties**

### Absorption

After a single dose,  $T_{max}$  was observed later (3h vs. typically about 1-2h) and plasma concentrations declined more gradually for the 300 mg PR tablet compared to an ibuprofen 200mg IR tablet, confirming the prolonged release characteristics of the 300 mg PR tablet.

After 12 hours, administration of a single dose of 2 x 300 mg PR tablets resulted in an overall comparable  $C_{max}$  and  $AUC_{0-12h}$  for S-ibuprofen, compared to the administration of ibuprofen 200 mg immediate release tablets every 4 hours (3 administrations).

For the steady state comparisons, administration of 2 x 300 mg PR tablets every 12 hours resulted in a 35% lower  $C_{max,ss}$ , a 20% lower  $AUC_{tau,ss}$  and a 31% higher  $C_{min,ss}$  and exposure over 24 hours ( $AUC_{0-24h,ss}$ ), compared to administration of ibuprofen 2 x 200 mg immediate release tablets every 8 hours.

Comparable patterns were observed after single dose and at steady state for the R-isomer and total ibuprofen. Overall, the pharmacokinetic parameters demonstrated similar exposure when comparing a single dose of PR compared to multiple doses of IR of the same total dose.

Administration of a single dose of 2 x 300 mg PR tablets with a high fat, high calorie breakfast, resulted in a  $T_{max}$  of about 5.5h and a 52% higher  $C_{max}$ . The higher S-ibuprofen peak plasma concentration is not expected to affect the safety of the product, as the concentration is in the range of the  $C_{max}$  following a standard single 400 mg dose of IR ibuprofen. Accordingly, the 300 mg PR tablets can be dosed independently of food intake.

### Distribution

Ibuprofen is 99% bound to plasma proteins. Ibuprofen is distributed throughout the whole body and diffuses into the synovial fluid. Limited data indicate that ibuprofen is excreted in breast milk in very low concentrations.

### Metabolism

Ibuprofen is metabolised in the liver mainly by hydroxylation and carboxylation into pharmacologically inactive metabolites. More than 90% of the dose is eliminated renally as metabolites and their conjugates. Less than 1% is excreted as intact ibuprofen.

### Elimination

The elimination half-life is approximately 2 hours.

## **5.3 Preclinical safety data**

No relevant information.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Core:

Hypromellose (E 464)  
Microcrystalline cellulose (E 460)  
Silica, colloidal hydrated (E 551)  
Croscarmellose sodium (E 468)  
Glycine (E 640)  
Stearic acid (E 570)

#### Coating:

Hypromellose (E 464)  
Titanium dioxide (E171)  
Macrogol  
Polysorbate 80 (E 433)

#### Polishing:

Carnauba wax (E 903)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years

### **6.4 Special precautions for storage**

Store below 30°C. Store in the original pack in order to protect from moisture.

### **6.5 Nature and contents of container**

Blister packs comprised of PVC/alu/polyamide with aluminium foil lidding in an outer carton containing 6, 8, 10, 12, 16, 20 and 24 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**

Reckitt Benckiser Ireland Ltd  
7 Riverwalk  
Citywest Business Campus  
Dublin 24  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA0979/081/001

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

Date of first authorisation: 12<sup>th</sup> May 2023

## **10 DATE OF REVISION OF THE TEXT**