Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mybufen Max 400 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg ibuprofen.
Excipients with known effect:
Each film-coated tablet contains 28.5 mg lactose (as monohydrate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
400 mg: White, oblong, biconvex film-coated tablets scored on both sides (length: 17 mm, width: 8 mm).
The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mybufen Max 400 mg film-coated tablets is indicated for:
- Short-term symptomatic treatment of mild to moderate pain (e.g. headache, toothache, muscular pain, dysmenorrhea) and/or fever of duration less than to 3 days.

Mybufen Max is indicated in adults and adolescents from 40 kg body weight (12 years of age and above).

4.2 Posology and method of administration

Posology

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

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

Mybufen Max 400 mg film-coated tablets:

Adults and adolescents from 12 years of age (≥ 40 kg body weight):
Initial dose 400 mg ibuprofen. If necessary, additional doses of 400 mg ibuprofen can be taken every 4-6 hours as necessary.. A total dose of 1200 mg ibuprofen should not be exceeded in any 24-hour period.

Special populations

Elderly:
NSAIDs (Nonsteroidal anti-inflammatories) should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. (See section 4.4, special warnings and special precautions for use). Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

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

Hepatic insufficiency (see section 5.2):

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

Paediatric population:
Mybufen Max 400 mg film-coated tablets is contraindicated in children younger than 12 years of age and in adolescents below 40 kg body weight due to lack of possibility of correct dosing.

Method of administration
Oral use.
The tablets should be swallowed whole with a glass of water.
It is recommended that patients with a sensitive stomach take Mybufen Max with food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with a history of hypersensitivity reactions (e.g. bronchospasm, asthma, rhinitis, angioedema or urticaria) associated with the use of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- Patients with severe heart failure (NYHA Class IV).
- Patients with severe liver failure or severe renal failure.
- Patients with unclarified blood-formation disturbances.
- Patients with cerebrovascular or other active bleeding.
- History of gastrointestinal bleeding or perforation associated with previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Patients with severe dehydration (caused by vomiting, diarrhea or insufficient fluid intake)
- Last three months of pregnancy.
- Children younger than 12 years of age and adolescents below 40 kg body weight because this tablet strength is not suitable due to lack of possibility of correct dosing.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest possible duration necessary to control symptoms (see Gastrointestinal and cardiovascular risks below).

Caution is required in patients with certain conditions, which may be made worse:

- systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis (see section 4.8)
- congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria)
- hypertension and/or cardiac impairment as renal function may deteriorate (see sections 4.3 and 4.8)
- renal impairment (see sections 4.3 and 4.8)
- hepatic dysfunction (see sections 4.3 and 4.8)
- directly after major surgery
- in patients who react allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of Mybufen Max
- in patients who suffer from hay fever, nasal polyps or chronic obstructive respiratory disorders as an increased risk exists for them of allergic reactions occurring. These may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria.

Gastrointestinal (GI) safety
The use with concomitant NSAIDs, including cyclo-oxygenase-2 specific inhibitors, increases risk of adverse reactions (see section 4.5) and should be avoided.

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

Gastrointestinal bleeding, ulceration and perforation:
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events. When GI bleeding or ulceration occurs in patients receiving ibuprofen, it is advised to withdraw the treatment.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses and 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 medicinal products (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, are advised to report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medicinal products which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet medicinal products such as acetylsalicylic acid (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).
NSAIDs may mask symptoms of infection and fever.

Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalized exanthematous pustulosis (AGEP), **which can be life-threatening or fatal,** have been reported in **association** with the use of **ibuprofen** (see section 4.8). **Most of these reactions occurred within** the first month.

If signs and symptoms suggestive of these reactions appear ibuprofen should be **withdrawn immediately and an alternative treatment considered (as appropriate).**
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 Mybufen Max in case of varicella.

Cardiovascular and cerebrovascular effects:
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

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

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

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

Kounis Syndrome

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.

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

Ibuprofen may temporarily inhibit the blood-platelet function (thrombocyte aggregation). Therefore, it is recommended to monitor patients with coagulation disturbances carefully.

In prolonged administration of Mybufen Max regular checking of the liver values, the kidney function, as well as of the blood count, is required.

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.

In general terms, the habitual intake of painkillers, particularly on combination of several pain-relieving active substances, 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. Therefore it should be avoided.

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.

The risk of renal failure is increased in dehydrated patients, the elderly and those taking diuretics and ACE inhibitors

Masking of symptoms of underlying infections
Mybufen Max 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 Mybufen Max 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.

Patients who report eye disorders during treatment with Ibuprofen should discontinue therapy and be submitted to eye examinations.

Mybufen Max contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

Lithium: NSAIDs may reduce lithium renal clearance, which will result in an increase of plasma levels and toxicity. If ibuprofen is prescribed to a patient receiving lithium therapy, a close monitoring on the levels of lithium should be conducted.

Methotrexate: NSAIDs may inhibit the tubular secretion of methotrexate and reduce its clearance. The administration of Mybufen Max within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.

Digoxin: The concomitant use of Mybufen Max with digoxin may increase serum levels of digoxin. A check of serum-digoxin is recommended.

Phenytoin: The concomitant use of Mybufen Max with phenytoin may increase serum levels of these medicinal products. A check of serum-phenytoin levels is recommended.

Cholestyramine: The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.

Ciclosporin: The risk of a kidney-damaging effect due to ciclosporin is increased through the concomitant administration of certain nonsteroidal anti-inflammatory drugs. This effect also cannot be ruled out for a combination of ciclosporin with ibuprofen.

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

Diuretics, Angiotensin Converting Enzyme Inhibitors (ACE), betareceptor-blockers and Angiotensin II Antagonists (AIIA): nonsteroidal anti-inflammatory drugs may reduce the efficacy of diuretics, as well as of other anti-hypertensive, betareceptor-blockers and diuretic medicinal products. Diuretics may also increase the NSAIDs nephrotoxicity risk. In some

patients with a decreased renal function (dehydrated patients or elderly with compromised renal function), the co-administration of an ACE, betareceptor-blockers or of an angiotensin II antagonist (AIIA) and inhibitors of cyclooxygenase 2 may progress to a deterioration of the renal function, including the possibility of acute renal failure, which is normally 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.

Potassium sparing diuretics: The concomitant administration of Mybufen Max and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended).

Other NSAIDs, including salicylates: The concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. The concomitant use of ibuprofen with other NSAIDs should therefore be avoided (see section 4.4).

Selective inhibitors of cyclooxygenase -2: The concomitant administration of ibuprofen with other NSAIDs, including selective inhibitors of cyclooxygenase -2 should be avoided due to the potential addictive effect (see section 4.4).

Corticosteroids: increase on the risk of ulceration or gastrointestinal bleeding (see section 4.4).

Anticoagulants: NSAIDs may increase the anticoagulants effects, such as warfarin (see section 4.4).

Anti-platelet medicinal products and selective serotonin reuptake inhibitors: increase on the risk of gastrointestinal bleeding (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).

Aminoglycosides: NSAIDs may reduce the elimination of aminoglycosides.

Ginkgo Biloba: it may boost the risk of bleeding.

Quinolone antibiotics: animal data report that NSAIDs, in combination with quinolone antibiotics, may increase the risk of convulsions. Patients taking NSAIDs and quinolones may present an increased risk of developing convulsions.

Sulfonylureas: NSAIDs may increase the effects of sulfonylureas. Rare cases of hypoglycemia were reported in patients with concomitant administration of sulfonylurea and ibuprofen. A check of blood-glucose values is recommended as a precaution on concomitant intake.

Tacrolimus: possible increased risk of nephrotoxicity when a NSAID is administered with tacrolimus.

Zidovudine: increased risk of hematological toxicity when a NSAID is administered with zidovudine. There is an evidence of an increased risk of hemarthrosis and hematoma in HIV (+) hemophilic patients receiving concomitant treatment with zidovudine and other NSAIDs.

CYP2C9 inhibitors: the concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazol and fluconazol (CYP2C9 inhibitors), it was demonstrated a higher exposure of S (+)-ibuprofen of around 80 to 100%. A dose reduction of ibuprofen should be considered when CYP2C9 inhibitors are concomitantly administered, especially when high doses of ibuprofen are administered with voriconazol or fluconazol.

Pentoxifylline: In patients receiving ibuprofen in combination with pentoxifylline may increase the risk of bleeding, it is recommended to monitor bleeding time.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from studies epidemiological suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of the 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 20th week of pregnancy onward, Mybufen 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, Mybufen should not be given unless clearly necessary. If Mybufen 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 Mybufen for several days from gestational week 20 onward. Mybufen 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:

- cardio-pulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above); - the mother and the neonate, at the end of the pregnancy, to:
- possible prolongation of bleeding time, an antiaggregant effect which may occur even at very low doses;
- inhibition of uterine contractions, resulting in delayed or prolonged labour.

Labour and delivery

Administration of ibuprofen is not recommended during labour and delivery. The onset of labour may be delayed and the duration increased with a greater bleeding tendency in both mother and child.

Consequently, Ibuprofen is contraindicated during the third trimester of pregnancy (see section 4.3 and 5.3).

Breastfeeding

In limited studies to date, ibuprofen appears in breast milk in very low concentrations. Mybufen is not recommended for use in nursing mothers.

Fertility

There is some evidence that drugs which inhibit cyclooxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

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 extend in combination with alcohol.

4.8 Undesirable effects

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

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 administration. Less frequently, gastritis, duodenal ulcer & gastric ulcer and gastrointestinal perforation have been observed.

Immune system disorders
Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of: non-specific allergic reaction and anaphylaxis, respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, very rarely, erythema multiforme, bullous dermatoses (including Stevens-Johnson syndrome, and toxic epidermal necrolysis)

Infections and infestations
Exacerbation of skin infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during the use of ibuprofen, the patient is therefore recommended to go to a doctor without delay.

Skin and subcutaneous tissue disorders
In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations" and section 4.4)

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

Please note that within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following frequency groupings, displayed by MedDRA frequency convention and system organ classification, for undesirable effects 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) and Not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Undesirable effects**
Infections and infestations	Uncommon	Rhinits
	Rare	Aseptic meningitis
Blood and lymphatic system disorders	Rare	Anaemia Leukopenia Thrombocytopenia Pancytopenia Agranulocytosis Eosinophilia Coagulopathy (changes in coagulation) Aplastic anemia Hemolytic anemia Neutropenia The first signs may be fever, sore throat, superficial wounds in the mouth, influenza-like complaints, severe lassitude, nosebleeds and skin bleeding. The blood count should be checked regularly in long-term therapy.
Immune system disorders	Uncommon	Hypersensitivity reactions with skin rashes and itching, as well as asthma attacks (possibly with drop in blood pressure) The patient is to be instructed to inform a doctor at once and no longer to take Mybufen Max in this case.

	Rare	Severe general hypersensitivity reactions (anaphylaxis). They may present as face oedema, swelling of the tongue, swelling of the internal larynx with constriction of the airways, respiratory distress, racing heart, drop in blood pressure up to life-threatening shock. If one of these symptoms occurs, which can happen even on first use, the immediate assistance of a doctor is required.
Metabolism and nutrition disorders	Very rare	Hypoglycemia Hyponatremia
Psychiatric disorders	Uncommon	Insomnia Depression Anxiety
	Rare	Confusion
Nervous system disorders	Common	Central nervous disturbances such as dizziness, headaches
	Uncommon	Paraesthesiae Somnolence
	Rare	Optic neuritis
Eye disorders	Uncommon	Visual disturbances
	Rare	Toxic optic neuropathy
Ear and labyrinth disorders	Uncommon	Tinnitus Loss of hearing Vertigo
Cardiac disorders	Very rare	Heart failure Myocardial infarction
	Not known	Kounis syndrome
Vascular disorders	Very rare	Hypertension
Respiratory, thoracic, and mediastinal disorders	Uncommon	Asthma Dyspnea Bronchospasm
Gastrointestinal disorders	Common	Gastro-intestinal complaints such as pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation and slight gastro-intestinal blood losses that may cause anaemia in exceptional cases.
	Uncommon	Gastrointestinal ulcers, gastritis, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4)
	Very rare	Pancreatitis
	Not known	Exacerbation of Colitis and Crohn's disease
Hepatobiliary disorders	Uncommon	Acute hepatitis Jaundice
	Very rare	Hepatic dysfunction Hepatic damage, particularly in long-term therapy 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, Bullous reactions including Stevens-Johnson Syndrome and toxic epidermal

		necrolysis (Lyell syndrome)). 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	Uncommon	Nephrotoxicity in various forms, e.g. Tubulointerstitial nephritis, nephrotic syndrome and 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 the HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

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, dizziness, vertigo and gastrointestinal bleeding may also occur. 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. Children may also develop myoclonic cramps. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to 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.
In serious poisoning metabolic acidosis may occur.

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

Treatment
Patient should immediately be transferred to a hospital.
Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Gastric emptying or oral administration of activated charcoal is indicated if the patient presents within one hour of the ingestion of more than 400 mg per kg of body weight. If the ibuprofen has already been absorbed, alkaline substances should be administered to promote the excretion of the acid ibuprofen in the urine. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Other measures may be indicated by the patient's clinical condition. Bronchodilators should be given for asthma. No specific antidote is available.
Renal and liver function should be closely monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, non-steroids; propionic acid derivatives
ATC code: M01AE01

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 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 (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).

5.2 Pharmacokinetic properties

Absorption:

Ibuprofen administered orally is absorbed quickly with approximately 80% in the gastrointestinal tract. Maximum plasma concentrations are reached (T-max) 1-2 hours after administration.
The administration of ibuprofen together with food delays the Tmax (from ± 2 h fasted to ± 3 h after eating), although this has no effect on the magnitude of absorption.

Distribution:
The estimated volume of distribution of ibuprofen after oral administration is 0.1 to 0.2 L/kg, with an extensively bound to plasma proteins around 99%.

Biotransformation:
Ibuprofen is rapidly metabolised in the liver by hydroxylation and carboxylation of the isobutyl group through CYP2C9 and CYP2C8, to two primary inactive. These together with unmetabolized ibuprofen, are excreted by the kidney either as such or as conjugates.

Elimination:
Ibuprofen is excreted mainly by the kidney and is practically complete 24 hours after the last dose. Approximately 10% is eliminated unaltered and 90% is eliminated as inactive metabolites, mainly as glucuronides. The elimination half-life of immediate release formulations is
approximately two hours

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 about1% in healthy volunteers. Severe impairment of renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis (see sections 4.2, 4.3 and 4.4).

Hepatic impairment
Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters.
In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) treated with racemic ibuprofen an average 2-fold prolongation of the half-life was observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of (R)-ibuprofen to the active (S)-enantiomer (see sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

In animal trials, the subchronic and chronic toxicity of ibuprofen showed up mainly in form of lesions and ulcerations in the gastrointestinal tract.

In vitro and *in vivo* studiesrevealed no clinically relevant evidence of a mutagenic potential of ibuprofen. Studies in rats and mice, no evidence of carcinogenic effects of ibuprofen was found.

Experimental studies in rat and rabbit have shown that ibuprofen crosses the placenta, without any evidence of teratogenic activity

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Hypromellose, Croscarmelose sodium, Lactose monohydrate, Microcrystalline cellulose, Pregelatinized starch (maize), Colloidal anhydrous silica, Magnesium stearate.
Film-coating: Hypromellose, Titanium dioxide (E171), Talc, Propylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

42 months

6.4 Special precautions for storage

Do not store above 30ºC

6.5 Nature and contents of container

Mybufen Max 400 mg film-coated tablet packed in Al-PVC/PVDC blisters in packs of 12 and 24 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Ibuprofen may pose a risk to the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Bluefish Pharmaceuticals AB
P.O. Box 49013
100 28 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER

PA1436/039/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd September 2022

10 DATE OF REVISION OF THE TEXT

October 2025