Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ryhogen 400 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 683.2 mg ibuprofen lysine equivalent to 400 mg ibuprofen.

Excipient(s) with known effect:
Each film-coated tablet contains 6.7 mg of isomalt.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Ryhogen 400 mg film-coated tablet: white to off-white to yellowish, oval, approx. 9.1 x 19.1 mm film-coated tablets, thickness approx. 6.4 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term symptomatic treatment of

- mild to moderate pain, such as headache, toothache and period pain
- fever

4.2 Posology and method of administration

Posology
Dosage is based on the information in the table below. The Ryhogen dose in adolescents depends on body weight (BW) or age, usually with 7 to 10 mg/kg of BW as a single dose, up to a maximum of 30 mg/kg BW as a total daily dose.
The respective dosing interval depends on the symptoms and the maximum total daily dose. It should not be less than 6 hours.

Body weight (age)	**Single dose in number of film-coated tablets**	**max. daily dose in number of film-coated tablets**
≥ 40 kg (Adolescents from 12 years and adults)	1 film-coated tablet (corresponding to 400 mg ibuprofen)	3 film-coated tablets (corresponding to 1 200 mg ibuprofen)

Method of administration
Oral use.
For short-term use only.

Ryhogen should be swallowed whole with a glass of water.

It is recommended that patients with a sensitive stomach take Ryhogen with food.

If Ryhogen is taken during or shortly after a meal, the onset of action may be delayed. If this is the case, do not take more Ryhogen than recommended in this section or before the end of the stated dosing interval.
If in adolescents this medicinal product is required for more than 3 days, or if symptoms worsen, a doctor should be consulted.

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

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

Special populations:

Elderly:
No special dose adjustment is required. Because of the possible adverse effect profile (see section 4.4), elderly people should be monitored with particular care.

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

Hepatic impairment (see section 5.2):
No dose reduction is required in patients with mild to moderate hepatic impairment. (For patients with severe hepatic impairment, see section 4.3).

Adolescents from 12 years
For use in adolescents, see also section 4.3.

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, rhinitis, angioedema or urticaria) associated with the intake of acetylsalicylic acid, ibuprofen or other non-steroidal anti-inflammatory drugs,
- Patients with severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV),
- History of gastrointestinal bleeding or perforation related to previous NSAIDs therapy,
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding),
- Cerebrovascular or other active bleeding,
- Unexplained disorders of haemopoiesis,
- Patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake),
- During the third trimester of pregnancy (see section 4.6),
- Children under 12 years or adolescents under 40 kg body weight, as this dose strength is not suitable due to the higher active substance content.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

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). There is also an increased risk of the sequelae of adverse effects.

Special care has to be taken in the following cases:

- Systemic lupus erythematosus or mixed connective tissue disease because of the increased risk of aseptic meningitis (see section 4.8)
- Congenital disturbance of porphyrin metabolism (e.g. acute intermittent porphyria)
- Gastrointestinal disorders and chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease) (see section 4.8)
- History of hypertension and/or cardiac insufficiency, as fluid retention and oedema have been reported in association with NSAID therapy
- Reduced renal function, as it may worsen (see sections 4.3 and 4.8)
- Hepatic dysfunction (see sections 4.3 and 4.8)
- Immediately after major surgical interventions
- Hay fever, nasal polyps or chronic obstructive airway disease, as there is then an increased risk of allergic reactions. These may occur as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria

- History of allergic reactions to other substances, as there is an increased risk of also having an allergic reaction to Ryhogen.

Other NSAIDs: The use of Ryhogen in combination with NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided.

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.
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 longer-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 Ryhogen. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Gastrointestinal bleeding, ulceration and perforation
Gastrointestinal 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.

The risk of GI, 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 GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI 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 (section 4.5).

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

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease), as their condition may be exacerbated.

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).

In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection. Thus, it is advisable to avoid use of ibuprofen in case of varicella.

Respiratory tract
Bronchospasm may occur in patients who suffer or have suffered from bronchial asthma or allergic diseases.

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

Ibuprofen, the active substance in Ryhogen, may temporarily inhibit the function of blood platelets (platelet aggregation). Therefore, patients with coagulation defects should be observed carefully.

In prolonged use of Ryhogen a periodical monitoring of hepatic and renal function as well as the blood count is necessary.

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.

Concomitant consumption of alcohol should be avoided when taking NSAIDs, since it may intensify side effects, especially if affecting the gastrointestinal tract or the central nervous system.

Kidneys
In general the habitual intake of analgesics, particularly the combination use of different analgesic substances, may cause permanent renal damage and a risk of renal failure (analgesics nephropathy).

Adolescents
There is a risk of renal impairment in dehydrated adolescents.

Reduced female fertility: See also section 4.6.

Ryhogen contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Ryhogen contains isomalt
Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of ibuprofen and the following substances should be avoided:

- Acetylsalicylic acid (ASA). 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).

- Other NSAIDs, including selective cyclooxygenase-2 inhibitors. The concurrent use of 2 or more NSAIDs should be avoided as this may increase the risk of side effects (see section 4.4).

Ibuprofen (like other NSAIDs) should be taken only with caution in combination with the following substances:

- Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin or heparin (see section 4.4).
- Phenytoin: co-administration of ibuprofen with phenytoin preparations can increase the serum level of phenytoin. Checking the serum phenytoin level is usually not necessary when used as directed (for a maximum of 4 days).
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4)
- Antihypertensive drugs (ACE inhibitors, beta-receptor blockers and angiotensin II antagonists) and diuretics, as NSAIDs can reduce the effect of these drugs. In some patients with reduced kidney function (e.g. dehydrated patients or elderly patients with reduced kidney function), the administration of ACE inhibitors, beta-receptor blockers and angiotensin II antagonists together with agents that inhibit cyclooxygenase can lead to further impairment of kidney function and through to acute renal failure. This is usually reversible. Such combination should therefore only be used with caution, especially in elderly patients. Patients should be adequately hydrated and periodic monitoring of the kidney values should be considered for the time immediately after the start of the combination therapy and periodically thereafter. Diuretics can increase the nephrotoxicity of NSAIDs.
- Cardiac glycosides e.g. digoxin: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma levels of cardiac glycosides. The co-administration of ibuprofen with digoxin preparations may increase digoxin plasma levels. Monitoring serum digoxin is usually not necessary when used as directed (max. over 4 days).
- Cyclosporine: increased risk of nephrotoxicity
- Lithium. There is evidence of a potential increase in lithium plasma levels. Monitoring the serum lithium level is usually not necessary when used as directed (max. over 4 days).
- Probenecid and sulfinpyrazone may cause a delay in the elimination of ibuprofen.
- Potassium-sparing diuretics: simultaneous administration may lead to hyperkalaemia. Checking the serum potassium is recommended.
- Methotrexate: there is evidence of a potential increase in methotrexate plasma levels. Taking ibuprofen within 24 hours before or after the administration of methotrexate can lead to increased methotrexate concentrations, resulting in increased toxicity.
- Zidovudine: there is evidence of an increased risk of haemarthrosis and haematoma in HIV positive haemophilia patients receiving concurrent treatment with zidovudine and ibuprofen.
- Sulphonylureas: clinical studies showed interactions between non-steroidal anti-inflammatory drugs and antidiabetic drugs (sulphonylureas). Although no interactions between ibuprofen and sulphonylureas have been described so far, monitoring of blood glucose levels is recommended as a precaution in case of concomitant use.
- Tacrolimus: possible elevated risk of nephrotoxicity with concomitant use.
- 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.
- 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.

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.

Animal studies have shown reproductive toxicity (see section 5.3).

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, which may progress to renal failure with oligohydramnios (**see above**);
- expose the mother and the neonate, at the end of the 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 section 4.3).

Breast-feeding
Ibuprofen and its degradation products can pass into breast milk in low concentrations. So far, no side effects have been reported for infants, so suspension of breastfeeding will usually not be necessary for the short-term treatment of pain and fever with the recommended dose.

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 on withdrawal of treatment.

4.7 Effects on ability to drive and use machines

As central nervous undesirable effects such as tiredness and dizziness may occur on use of Ryhogen at higher dosage, 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 includes all known side effects during treatment with ibuprofen, including those during high-dose long-term therapy in rheumatism patients. Frequency data beyond very rare reports refer to short-term use up to daily doses of a maximum of 1 200 mg ibuprofen for oral dosage forms and maximum 1 800 mg for suppositories.

With the following adverse drug reactions, it must be taken into account that they are mostly dose-dependent and vary inter-individually.

The ibuprofen-related adverse effects listed below have been sorted by system organ class and frequency. The frequency data are based on the following categories: 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). Within the frequency groups, the undesirable effects are ranked according to decreasing severity.

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Undesirable effects are mostly dose-dependent. Especially the risk for the occurrence of gastrointestinal bleeding depends on the dosage range and duration of the treatment. 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.

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).

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.

If symptoms of infection appear or worsen while taking ibuprofen, the patient is advised to consult a doctor without delay. It is to be investigated whether there is an indication for anti-infective/antibiotic therapy.

In long-term therapy, the blood count should be checked regularly.

The patient must be instructed to inform the doctor immediately if symptoms of a hypersensitivity reaction occur and to stop taking ibuprofen. Immediate medical attention is required if these symptoms occur, which can happen even on first use.

The patient must be instructed to discontinue the medicinal product and consult a doctor immediately if severe pain occurs in the upper abdomen or if melaena or haematemesis occurs.

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Very rare	Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis). In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection.
Blood and lymphatic system disorders	Very rare	Haematopoietic disorders (anaemia, leucopoenia, thrombocytopenia, pancytopenia, agranulocytosis). The first symptoms or signs may include: fever, sore throat, surface mouth ulcers, flu-like symptoms, severe exhaustion, nasal and skin bleeding and bruising. In these cases, the patient should be advised to discontinue the medicine, refrain from any self-medication with analgesics or antipyretics and consult a doctor.
Immune system disorders		Hypersensitivity reactions consisting of[1]
	Uncommon	Urticaria and pruritus
	Very rare	Severe hypersensitivity reactions. They can manifest as facial oedema, swelling of the tongue, internal laryngeal swelling, dyspnoea, tachycardia, fall of blood pressure(anaphylaxis, angioedema or severe shock). Worsening of asthma
	Not known	Respiratory reactions (asthma, bronchospasm or dyspnoea)
Psychiatric disorders	Very rare	Psychotic reactions, depression
Nervous system disorders	Uncommon	Central nervous system disturbances such as headaches, dizziness, insomnia, agitation, irritability, tiredness
	Very rare	Aseptic meningitis[2]
Eye disorders	Uncommon	Visual disturbances
Ear and labyrinth disorders	Rare	Tinnitus
	Not known	Hearing impairment
Cardiac disorders	Very rare	Heart failure, palpitations, oedema, myocardial infarction
	Not known	Kounis syndrome
Vascular disorders	Very rare	Hypertension, vasculitis
Gastrointestinal disorders	Very common	Gastrointestinal complaints such as abdominal pain, nausea, dyspepsia, diarrhoea, flatulence, constipation, heartburn, vomiting and minor blood loss in the gastrointestinal tract, which in exceptional cases may cause anaemia.

	Uncommon	Gastrointestinal ulcers, perforation or gastrointestinal bleeding, ulcerative stomatitis, worsening of colitis and Crohn's disease (see section 4.4), gastritis
	Very rare	Oesophagitis, formation of intestinal diaphragm-like strictures, pancreatitis
Hepatobiliary disorders	Very rare	Liver dysfunction, liver damage, especially in long-term use, liver failure, acute hepatitis
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 (Lyell's syndrome)), alopecia
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalized exanthematous pustulosis (AGEP), photosensitivity reactions
Renal and urinary disorders	Rare	Kidney tissue damage (papillary necrosis) and increased uric acid concentrations in the blood
	Very rare	Formation of oedemas especially in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis which can be accompanied by acute renal insufficiency.
Investigations	Rare	Decreased haemoglobin levels

Description of adverse reactions:
[1] Hypersensitivity reactions have been observed during ibuprofen treatment. These may include:

- non-specific allergic reactions and anaphylaxis
- respiratory effects such as asthma, exacerbation of asthma, bronchospasm, dyspnoea
- various skin manifestations, including different types of rashes, pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme)

[2] The pathogenic mechanism of drug-induced aseptic meningitis is not yet fully understood. However, the data available for NSAIDs indicate an immune reaction (temporal relationship with intake, disappearance of symptoms after discontinuation). Interestingly, symptoms of aseptic meningitis (such as neck stiffness, headache, nausea, vomiting, fever or clouding of consciousness) have occasionally been observed during treatment with ibuprofen in patients with existing autoimmune diseases (such as systemic lupus erythematosus or mixed connective tissue disease).

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 www.hpra.ie.

4.9 Overdose

In children, taking more than 400 mg may cause symptoms. In adults, the dose-response relationship is less clear. The half-life in case of overdose is 1.5-3 hours.

Symptoms
Most patients who have taken clinically significant amounts of NSAIDs will not get more than nausea, vomiting, abdominal pain or more rarely diarrhoea. Tinnitus, headaches and gastrointestinal bleeding are also possible. In more severe poisoning, toxicity manifests itself in the central nervous system. It presents as vertigo, dizziness, light-headedness, occasionally agitation, clouding of consciousness or coma. Sometimes patients develop cramps. In serious poisoning, hyperkalaemia and metabolic acidosis may occur; the prothrombin time (INR) may be prolonged, probably due to interaction with circulating coagulation factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur. In asthmatics, an exacerbation of asthma is possible. Nystagmus, blurred vision and unconsciousness.
Prolonged use at higher than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia.

Treatment
Immediate transfer to hospital. No specific antidote is available.

Treatment should be symptomatic and supportive and include keeping the airways clear and monitoring cardiac and vital functions until stabilisation is achieved. Within one hour of ingestion of a potentially toxic amount, oral administration of activated charcoal or gastric lavage may be considered if the patient is responsive. If ibuprofen has already been absorbed, alkaline substances can be given to increase the excretion of ibuprofen as acid in the urine. Frequent or prolonged convulsions should be treated with intravenous diazepam or lorazepam. Bronchodilators should be given for asthma attacks. Poison control centres can be asked for medical advice.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: non-steroidal anti-inflammatory and antirheumatic drugs; propionic acid derivatives
ATC code: M01AE01

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that has been shown to be effective via prostaglandin synthesis inhibition in standard animal models of inflammation, swelling and fever. In addition ibuprofen has a reversible inhibitory effect on 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 hours 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).

The clinical efficacy of ibuprofen has been demonstrated for pain associated with headache, toothache, dysmenorrhoea, and fever.

5.2 Pharmacokinetic properties

When administered orally, ibuprofen is partially absorbed in the stomach and then completely absorbed in the small intestine.

After hepatic metabolisation (hydroxylation, carboxylation), the pharmacologically ineffective metabolites are completely eliminated mainly via the kidneys (90%), but also in bile. Maximum plasma levels are reached after oral administration of ibuprofen acid after 1 – 2 hours.

In a pharmacokinetics study, a mean ibuprofen plasma level of 11.28 µg/ml was reached 10 minutes after intake of ibuprofen lysinate (400 mg ibuprofen corresponding to 684 mg ibuprofen-DL-lysine (1:1)) on an empty stomach. Maximum plasma levels were recorded 37.8 min (0.63 h) after ingestion.

The elimination half-life is 1.8 to 3.5 hours in healthy individuals and those with liver and kidney disease, and plasma protein binding is about 99%.

Limited studies showed that ibuprofen passes into breast milk at very low doses.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans with ibuprofen based on conventional studies of genotoxicity and carcinogenic potential.

The subchronic and chronic toxicity of ibuprofen was demonstrated in animal experiments mainly in the form of lesions and ulcers in the gastrointestinal tract.

Ibuprofen inhibited ovulation in rabbits and impaired implantation in different animal species (rabbit, rat, mouse). Experimental studies have shown that ibuprofen crosses the placental barrier. An increased incidence of malformations (e.g. ventricular septal defects) was observed at doses toxic to the mother.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Sodium starch glycolate type A
Povidone K30
Magnesium stearate

Tablet coating:
Hypromellose
Isomalt (E953)
Calcium carbonate
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

The tablets are packed into PVC/PVDC//Alu blisters.

Pack sizes: 20 film-coated tablets

6.6 Special precautions for disposal and other handling

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Zentiva k.s.
U Kabelovny 130
Dolni Mecholupy
Prague
102 00
Czech Republic

8 MARKETING AUTHORISATION NUMBER

PA1701/015/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 9th of May 2025

10 DATE OF REVISION OF THE TEXT