

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen (als lysine) Mylan OTC 200 mg, filmomhulde tabletten
Ibuprofen (als lysine) Mylan OTC 400 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of ibuprofen (as lysine)
Each tablet contains 400 mg of ibuprofen (as lysine)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, film-coated, round, biconvex, bevelled edge tablet imprinted with “M” over “IL1” in black ink on one side of the tablet and blank on the other side.

Dimension: 10.5mm ± 0.3mm.

White to off-white, film-coated, oval biconvex, bevelled edge tablet imprinted with “M IL2” in black ink on one side of the tablet and blank on the other side

Dimension: 17.9mm ± 0.3mm x 9.2mm ± 0.3mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic treatment of mild to moderate pain, such as headache, dental pain, period pain and fever and pain in the common cold.

4.2 Posology and method of administration

Adults and adolescents ≥ 40 kg body weight (12 years of age and above):

[200 mg only]

Initial dose: 200 mg or 400 mg. If necessary, an additional dose of 1 to 2 tablets (200 mg to 400 mg) may be taken. The corresponding dosing interval should be chosen based on the symptoms and the recommended daily maximum dose. It should not be less than 6 hours for a 400 mg dose, and not less than 4 hours for a 200 mg dose. Do not exceed 1200 mg dose in any 24 hour period.

[400 mg only]

Initial dose: 400 mg. If necessary, an additional dose of 400 mg may be taken. The corresponding dosing interval should be chosen based on the symptoms and the recommended daily maximum dose. It should not be less than 6 hours for a 400 mg dose. Do not exceed 1200 mg dose in any 24 hour period.

Paediatric population

[200 mg only]

Children over 6 years (20 kg – 40 kg body weight):

Ibuprofen should only be used in children with a body weight of at least 20 kg.

The maximum daily dose of ibuprofen is 20 – 30 mg of ibuprofen per kg body weight, divided into 3 to 4 individually administered doses with a dosage interval of 6 to 8 hours. The recommended maximum daily dose should not be exceeded. A maximum dosage of 30 mg/kg of ibuprofen within a 24 hour period should not be exceeded.

The following dosage information applies:

| Body weight | Single dose | Maximum daily dose |
|--------------------|-----------------------------|-------------------------------------|
| 20 kg – 29 kg | 1 tablet (200 mg ibuprofen) | 3 tablets (equals 600 mg ibuprofen) |
| 30 kg – 39 kg | 1 tablet (200 mg ibuprofen) | 4 tablets (equals 800 mg ibuprofen) |

If in children aged from 6 years and in adolescents this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Children under 6 years

Ibuprofen is contraindicated in children under 6 years old.

[400 mg only]

Ibuprofen is contraindicated in adolescents under 40 kg body weight or in children under 12 years.

If in children aged from 12 years and in adolescents this medicinal product is required for more than 3 days, 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). Only for short-term use

If this product is required for more than 3 days in the case of fever or for more than 4 days for the treatment of pain or if the symptoms worsen the patient is advised to consult a doctor.

Elderly patients

No special dose adjustment is necessary. Elderly patients should be monitored particularly carefully due to the possible undesirable effect profile (see section 4.4).

Patients with sensitive stomachs

Patients with sensitive stomachs should take ibuprofen during a meal.

Taking ibuprofen after a meal may delay the onset of its action. If this should occur, no additional ibuprofen should be taken than specified in section 4.2 (Posology), or until the corresponding dosage interval has expired.

Patients with renal impairment

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

Patients with hepatic impairment

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

Method of administration:

For oral administration and short-term use only. Ibuprofen tablets are swallowed whole with plenty of water. Do not chew the tablets.

4.3 Contraindications

Ibuprofen is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- who have previously shown hypersensitivity reactions (e.g. bronchospasm, angioedema, rhinitis, urticaria or asthma) in response to acetylsalicylic acid (ASA) or other non steroidal anti-inflammatory drugs (NSAIDs),
- with active or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding),
- with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy,
- with severe hepatic insufficiency, severe renal insufficiency or severe heart failure (NYHA Class IV) (see section 4.4),
- [200 mg only] children under 20 kg body weight (about 6 years of age)
- [400 mg only] adolescents under 40 kg body weight or children below 12 years of age
- with cerebrovascular or other active bleeding,
- with unclarified blood-formation disturbances,
- with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake),
- during the last trimester of pregnancy (see section 4.6).

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 effects on gastrointestinal tract and cardiovascular system).

Caution should be exercised during administration of ibuprofen in patients suffering from the following conditions, which may be made worse:

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

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).

Respiratory:

Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.

Other NSAIDs:

The use of ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors increases the risk of adverse reactions and should be avoided (see section 4.5).

Renal:

Renal impairment as renal function may further deteriorate (see sections 4.3 and 4.8).

In general terms, the habitual intake of painkillers particularly the 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.

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

Hepatic:

Hepatic dysfunction (see sections 4.3 and 4.8).

It is suitable to discontinue the therapy with ibuprofen when deterioration of the liver functions occurs in connection with its administration. After discontinuation of the treatment the health state usually normalises. Occasional monitoring of glycaemia is also suitable.

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.

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 or smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) and in long-term treatment 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.

Impaired female fertility:

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

Gastrointestinal (GI):

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).

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 ulcers, 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 ASA, or other active substances 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 ASA (see section 4.5).

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

Severe skin reactions:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, 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. Ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can cause serious cutaneous and soft tissue 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 the use of ibuprofen in case of varicella.

Masking of symptoms of underlying infections

Ibuprofen (als lysine) Mylan OTC 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 (als lysine) Mylan OTC 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.

Other notes

Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of hypersensitivity reaction after taking/administering ibuprofen 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 ibuprofen 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. MOH must not be treated by increasing the dosage of the medicinal product.

During treatment with ibuprofen, some cases with symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed in patients with existing autoimmune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

Consumption of alcohol should be avoided since it may intensify side effects of NSAIDs, especially those affecting the gastrointestinal tract or the central nervous system.

Patients on ibuprofen should report to their doctor signs or symptoms of gastro-intestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain or oedema.

If vision problems, blurred vision, scotomata or malfunctions of colour perception appear, interruption of the treatment is necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should be avoided in combination with:

Acetylsalicylic acid

Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential for 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 salicylates and cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs as this may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. (see section 4.4).

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

Diuretics, ACE inhibitors, beta-receptor blockers and angiotensin-II antagonists:

NSAIDs may reduce the effect of diuretics and other antihypertensive medicinal products. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of ACE inhibitors, beta-receptor blockers or angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

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

Corticosteroids: Increased risk of adverse reactions, especially of the gastrointestinal tract (gastrointestinal ulceration or bleeding (see section 4.4)).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4)

Digoxin: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma digoxin levels. A check of serum-digoxin is not as a rule required on correct use (maximum over 4 days).

Phenytoin: The concomitant use of ibuprofen with phenytoin preparations may increase serum levels of phenytoin. A check of serum-phenytoin levels is not as a rule required on correct use (maximum over 4 days).

Lithium: There is evidence for potential increases in plasma levels of lithium. A check of serum lithium is not as a rule required on correct use (maximum over 4 days).

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

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Sulfinpyrazone: Medicinal products that contain sulfinpyrazone may delay the excretion of ibuprofen.

Probenecid: Medicinal products that contain probenecid may reduce the clearance of NSAIDs and may increase their serum concentration.

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

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. Blood counts 1-2 weeks after starting use together are recommended.

There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Sulfonylureas: NSAIDs can either increase or decrease the hypoglycemic effect of sulphonylureas. Caution is advised in case of simultaneous treatment.

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.

Alcohol, bisphosphonates, oxpentifylline (pentoxifylline) and sulfinpyrazone: May potentiate the GI side-effects and the risk of bleeding or ulceration.

Baclofen: Elevated baclofen toxicity.

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 raise concern about 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 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, ibuprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

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

renal dysfunction (see above)the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

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

Breast-feeding

Ibuprofen and its metabolites can pass in low concentrations 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 and fever at the recommended dose. Safety after long term use has not been established.

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

Ibuprofen has no or negligible influence on the ability to drive and use machines. However, since at high dosage side effects such as fatigue, somnolence, vertigo and visual disturbances (reported as uncommon) may be experienced, the ability to drive a car or operate machinery may be impaired in individual cases. This effect is potentiated by simultaneous consumption of alcohol.

4.8 Undesirable effects

Possible side effects are those experienced with ibuprofen acid.

Undesirable effects are mostly dose-dependent and vary interindividually. Especially the risk for the occurrence of gastrointestinal bleeding depends on the dosage range and duration of the treatment. Other known risk factors, see section 4.4.

The following undesirable effects are related to short-term use of low-dose ibuprofen (up to 1,200 mg per day for mild to moderate pain and fever. Other undesirable effects may occur with treatment for other indications or prolonged use.

Undesirable effects associated with ibuprofen are listed in the table below 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). In each frequency category, the undesirable effects are presented in order of decreasing frequency.

| System organ class | Frequency | Undesirable effects |
|--------------------------------------|------------------|--|
| Blood and lymphatic system disorders | Very rare | Haematopoietic disorders ¹ |
| Immune system disorders | Uncommon | Hypersensitivity reactions with urticaria and pruritus ² |
| | Very rare | Severe hypersensitivity reactions. Possible symptoms: facial, tongue and laryngeal swelling, oedema, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock) ² |
| Psychiatric disorders | Rare | Confusion, hallucinations |
| | Not known | Psychotic disorder, depression |
| Nervous system disorders | Common | Headache, somnolence, vertigo, fatigue, agitation, dizziness, insomnia, irritability |
| | Very rare | Aseptic meningitis ³ |
| Eye disorders | Not known | Amblyopia ⁴ , blurred vision ⁴ , reduced vision ⁴ |
| Ear and labyrinth disorders | Rare | Tinnitus |
| Cardiac disorders | Very rare | Palpitations, myocardial infarction, acute pulmonary oedema |
| | Not known | Heart failure, oedema |
| Vascular disorders | Not known | Arterial hypertension |
| | Uncommon | Rhinitis |

| | | |
|---|-------------|---|
| Respiratory, thoracic and mediastinal disorders | Very rare | Asthma exacerbation |
| | Not known | Airway reactivity such as bronchospasm, asthma or dyspnoea ² |
| Gastrointestinal disorders | Very common | Heartburn, abdominal pain, nausea, dyspepsia, diarrhoea, flatulence, constipation and vomiting ⁵ |
| | Common | Peptic ulcer ⁶ , gastrointestinal perforation or bleeding ⁶ , melaena, haematemesis, mouth ulcer, colitis |
| | Uncommon | Gastritis |
| | Very rare | Oesophagitis, pancreatitis, intestinal strictures |
| | Not known | Exacerbation of colitis and Crohn's disease ⁷ |
| Hepatobiliary disorders | Very rare | Liver dysfunction, liver damage, especially in long term use, liver failure, acute hepatitis, jaundice ⁸ |
| Skin and subcutaneous tissue disorders | Uncommon | Photosensitivity, skin rash ² |
| | Very rare | Severe forms of skin reactions with soft tissue complications may occur during varicella infections, necrotising fasciitis, exfoliative dermatitis, rash with blistering, including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis ² |
| | Not known | Alopecia ⁹ , Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP). |
| Renal and urinary disorders | Uncommon | Development of oedema, especially in patients with arterial hypertension or renal insufficiency, nephrotic syndrome and interstitial nephritis which can be associated with renal failure ¹⁰ |
| | Rare | Renal papillary necrosis ¹⁰ |
| | Very rare | Acute renal failure ¹⁰ dysuria |
| Reproductive system and breast disorders | Not known | Menstrual cycle disturbances |
| Investigations | Rare | Increase of blood urea nitrogen, serum transaminases and alkaline phosphatase, decrease in haemoglobin and haematocrit values, inhibition of platelet aggregation, decrease of serum calcium, increase in serum uric acid. |
| | Not known | Prolonged bleeding ¹¹ |

Description of selected adverse reactions

¹ Examples including anaemia, leukopenia, thrombocytopenia, pancytopenia and agranulocytosis. First signs: fever, sore throat, superficial mouth ulcers, flu-like symptoms, symptoms of exhaustion, nosebleeds and bleeding of the skin.

² Hypersensitivity reactions: These may include (a) non-specific allergic reactions and anaphylaxis, (b) airway reactivity, including asthma, asthma exacerbation, bronchospasm and dyspnoea, or (c) various skin reactions, including urticaria, exanthema and purpura, uncommonly associated with pruritus. Angioedema and, in rare cases, exfoliative and blistering dermatoses, including toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme have been reported. Some reactions including meningial

irritation and lethargy are considered to be associated with hypersensitivity reactions. Systemic lupus erythematosus and other collagen diseases are risk factors for severe cases of generalised hypersensitivity reactions. Generalised hypersensitivity reactions are uncommon. Symptoms may include fever with rash, abdominal pain, headache, nausea and vomiting, signs of liver damage and even meningeal symptoms. In rare cases, ibuprofen can trigger bronchospasm in predisposed patients.

³ The pathogenic mechanism of drug-induced aseptic meningitis is not fully understood. The data available on NSAID-related aseptic meningitis are however suggestive of a hypersensitivity reaction (due to a time relationship between administration of the medicinal product and disappearance of the symptoms after treatment withdrawal). Isolated cases of symptoms of aseptic meningitis such as nuchal rigidity, headache, nausea, vomiting, fever and disorientation have been observed during treatment with ibuprofen of patients with existing autoimmune diseases (systemic lupus erythematosus and mixed connective tissue disease).

⁴ Reversible effects have been reported.

⁵ The most common undesirable effects are gastrointestinal undesirable effects.

⁶ Uncommonly fatal, especially in elderly patients. See Special warnings and precautions for use

⁷ See section 4.4.

⁸ Hepatotoxic reactions may occur as part of generalised hypersensitivity reactions.

⁹ Reversible alopecia in black women has been reported.

¹⁰ Especially on long-term use, associated with elevated serum urea concentrations, decreased urine excretion and oedema. Including papillary necrosis.

¹¹ Ibuprofen may prolong the bleeding time at doses exceeding 1000 mg per day.

Clinical trial and epidemiological data suggest that the use of ibuprofen, particularly at high doses (2400 mg per day) and with prolonged use, may be associated with a slightly elevated risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

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 national reporting system listed in Appendix V [to be completed nationally].

4.9 Overdose

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear-cut. The half-life in overdose is 1.5-3 hours.

Symptoms

Significant overdoses are generally well tolerated as long as no other medicinal products are involved. 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 dizziness, drowsiness, occasionally excitation and disorientation, loss of consciousness (in children also myoclonic seizures) 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. Furthermore, hypotension, respiratory depression and cyanosis are also possible.

Management

No specific antidote is available. Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. If need, correction of the serum electrolyte balance may be performed. Forced diuresis and haemodialysis are not useful, as ibuprofen is extensively metabolised and is almost fully protein-bound. Gastric emptying or oral administration of activated charcoal is indicated if the patient presents within one hour of ingestion of a large toxic quantity. In the event of gastrointestinal bleeding, activated charcoal may hinder endoscopy. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Bronchodilators should be given for asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivative.

ATC code: M01A E01

Mechanism of action

Ibuprofen lysine is the lysine salt of ibuprofen, a propionic acid derivative. Ibuprofen is a non-steroidal 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.

Following oral administration, ibuprofen lysine dissociates to ibuprofen acid and lysine. Lysine has no recognised pharmacological activity. The pharmacological properties of ibuprofen lysine, therefore, are the same as those of ibuprofen acid.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics 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

Most pharmacokinetic data obtained following the administration of ibuprofen acid also apply to ibuprofen lysine.

On oral application, ibuprofen is partly absorbed in the stomach and then completely in the small intestine.

Following hepatic metabolism (hydroxylation, carboxylation), the pharmacologically inactive metabolites are completely eliminated, mainly renally (90 %), but also with the bile. The elimination half-life in healthy individuals and those with liver and kidney diseases is 1.8 - 3.5 hours, plasma-protein binding about 99 %.

Peak plasma concentrations occur 1-2 hours after oral administration of a normal-release pharmaceutical form of ibuprofen acid. However, ibuprofen is more rapidly absorbed from the gastrointestinal tract following the oral administration of ibuprofen lysine tablets.

No specific difference in pharmacokinetic profile is observed in the elderly.

5.3 Preclinical safety data

The subchronic and chronic toxicity of ibuprofen in animal experiments was observed principally as lesions and ulcerations in the gastrointestinal tract. *In vitro* and *in vivo* studies gave no clinically relevant evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found. Ibuprofen led to inhibition of ovulation in rabbits as well as disturbance of implantation in various animal species (rabbit, rat, mouse). Experimental studies have demonstrated that ibuprofen crosses the placenta, for maternally toxic doses, an increased incidence of malformations (e.g. ventricular septal defects) was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Cellulose, microcrystalline (E460)
Silica colloidal anhydrous (E551)
Crospovidone (E1202)
Povidone (E1201)
Magnesium stearate (E572)
Talc (E553b)

Tablet coating

Polyvinyl alcohol hydrolysed (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)

Printing ink

Shellac (E904)
Iron oxide black (E172)
Ammonium hydroxide (E527).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

Bottles: Use within 60 days of opening. Once open, keep bottle tightly closed.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottle pack comprises of white opaque HDPE bottle with white opaque cap with aluminium induction sealing liner wad and desiccant (silica gel).

Note: The HDPE bottle pack may be placed in an outer cardboard carton based on commercial requirement.

Dispensing pack: HDPE bottle pack comprises of white opaque HDPE bottle with white opaque cap with aluminium induction sealing liner wad and desiccant (silica gel).

Note: The HDPE bottle pack may be placed in an outer cardboard carton based on commercial requirement.

Blister pack comprises of white opaque PVC laminated with Aclar on one side and hard tempered aluminium foil coated with VMCH heat seal lacquer on the other side.

Cold form blister pack comprises of cold form laminate (aluminium foil laminated to oriented polyamide on one side and laminated to PVC on the other side i.e. OPA / Al / PVC) on one side and hard tempered aluminium foil coated with VMCH heat seal lacquer on the other side.

Pack sizes:

Blisters: 2, 4, 6, 10, 12, 16, 20, 24, 30, 36, 48, 50, 100, 200.

Bottles: 48, 100, 200 (dispensing pack).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable

7. MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Ltd
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ierland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 111362- Ibuprofen (als lysine) Mylan OTC 200 mg, filmomhulde tabletten

RVG 111363- Ibuprofen (als lysine) Mylan OTC 400 mg, filmomhulde tabletten

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 9 september 2013

Datum van laatste verlenging: 23 juli 2018

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 4.6: 16 maart 2023