SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen (als lysine) HTP 200 mg, filmomhulde tabletten
Ibuprofen (als lysine) HTP 400 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Product name> 200 mg
Each film-coated tablet contains ibuprofen 200 mg (as 342 mg ibuprofen lysine).
<Product name> 400 mg
Each film-coated tablet contains ibuprofen 400 mg (as 684 mg ibuprofen lysine).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets
<Product name> 200 mg
Pale red, round, biconvex, film coated tablets, plain on both sides with diameter of nucleus 11 mm.
<Product name> 400 mg
White to almost white, capsule shape, biconvex film-coated tablets, plain on both sides, with dimensions of nucleus 19x10 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Product name> is indicated in short-term symptomatic treatment of mild to moderate pain such as headache, dental pain and menstrual pain and/or fever.
<Product name> is indicated in adults and adolescents from 40 kg body weight (12 years of age and above).

4.2 Posology and method of administration

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

Posology
<Product name> 200 mg
Adults and adolescents from 40 kg body weight (12 years of age and above)
The initial dose is 200 to 400 mg, and then, if necessary, the dose may be repeated every 6 hours.
The maximal daily dose of 1 200 mg (6 tablets) should not be exceeded in any 24 hours.
<Product name> 400 mg

Adults and adolescents from 40 kg body weight (12 years of age and above)
The initial dose is 400 mg, and then, if necessary, the dose may be repeated every 6 hours. The maximal daily dose of 1 200 mg should not be exceeded in any 24 hours.

If in adults this medicinal 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.

If in adolescents (12 years of age and above) this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Elderly
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 renal/hepatic impairment
In patients with mild to moderate renal or hepatic impairment, the lowest effective dose and caution should always be taken (patients with severe renal or hepatic impairment, see section 4.3).

Paediatric population
<Product name> is not intended for use in adolescents below 40 kg body weight or children younger than 12 years of age.

Method of administration
For oral use.
The tablets should be taken with a glass of water.
It is recommended that patients with a sensitive stomach take <Product name> with food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- History of gastrointestinal bleeding or perforation related to previous non-steroidal anti-inflammatory drugs (NSAIDs) therapy.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Patients with a history of hypersensitivity reactions (e.g. asthma, bronchospasm, rhinitis, angioedema or urticaria) associated with the use of acetylsalicylic acid or other NSAIDs.
- Severe hepatic failure.
- Severe renal failure.
- Severe heart failure (NYHA Class IV).
- Cerebrovascular haemorrhage or other active haemorrhage.
- Severe dehydration (e.g. caused by vomiting, diarrhoea or insufficient fluid intake).
- Last three months of pregnancy.

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 Gastrointestinal and Cardiovascular risks below).

Caution is required in patients with certain conditions, which may be made worse:
- Systemic Lupus Erythematosus (SLE) or mixed connective tissue disease – increased risk of aseptic meningitis (see section 4.8);
- Congenital disorders of porphyrin metabolism (e.g. acute intermittent porphyria);
- Mild to moderate renal impairment;
- Mild to moderate hepatic impairment;
- Directly after major surgery;
- In patients who react allergically to other substances an increased risk of hypersensitivity reactions occurring also exists for them on use of <Product name>;
- 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.

Cardiovascular and cerebrovascular effects

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

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2 400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1 200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2 400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2 400 mg/day) are required.

Cases of Kounis syndrome have been reported in patients treated with ibuprofen. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Gastrointestinal safety

The concomitant use of ibuprofen with other NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

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).

Gastrointestinal bleeding, ulceration or perforation: Gastrointestinal bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without any warning symptoms or a previous history of serious gastrointestinal events. The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment

on the lowest dose available. Combination therapy with protective 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 4.5).
Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment.
Caution should be advised in patients receiving concomitant medicinal products which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or antiplatelet medicinal products such as acetylsalicylic acid (see section 4.5).
When gastrointestinal 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 (see section 4.8).

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

If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. Thus, it is advisable to avoid use of <Product name> in case of varicella.

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.

Visual disturbances
In case of visual disturbances appearing during treatment with ibuprofen, the medicinal product should be suspended immediately and the patient should be submitted to ophthalmological examination.

Respiratory effects
Bronchospasm may precipitate in patients with symptoms or history of bronchial asthma or allergic diseases.

Other information
Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are very rarely observed. At the first signs of a hypersensitivity reaction following use of ibuprofen, treatment must be discontinued. Medically required measures, in line with the symptoms, must be initiated by

specialist personnel.

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

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

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

In general, habitual intake of analgesics, especially when several analgesic medicinal products are combined, may lead to permanent renal damage, with a risk of renal failure (analgesic nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore the combined use of several analgesics should be avoided.

When using NSAIDs, adverse reactions, particularly those affecting the gastrointestinal tract or central nervous system, may be enhanced by concomitant consumption of alcohol.

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

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

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 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 effects of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional use (see section 5.1).

Other NSAIDs including cyclo-oxygenase-2-selective inhibitors: Concomitant use of two or more NSAIDs should be avoided, as this may increase the risk of adverse reactions.

Ibuprofen should be used with caution in combination with:

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

Antihypertensives (ACE inhibitors, beta-receptor blockers and Angiotensin II Antagonists) and

diuretics: since NSAIDs may diminish the effects of these medicinal products. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor, beta-receptor blockers or Angiotensin II antagonist and medicinal products that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Corticosteroids: Concomitant use of corticosteroids with ibuprofen may increase the risk of gastrointestinal ulceration or bleeding (see section 4.4).

Antiplatelet medicinal products and selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of NSAIDs and antiplatelet medicinal products or selective serotonin reuptake inhibitors increase the risk of gastrointestinal bleeding (see section 4.4).

Digoxin, phenytoin, lithium: Concomitant use of <Product name> with digoxin, phenytoin or lithium preparations can increase the serum level of these medicinal products. Monitoring of serum lithium levels, serum digoxin levels and serum phenytoin levels is not generally required when used as directed (over 3 or 4 days maximum).

Methotrexate: NSAIDs may inhibit the tubular secretion of methotrexate and reduce its clearance. Administration of ibuprofen within 24 hours before or after methotrexate administration can lead to increased concentration of methotrexate and an increase in its toxic effect.

Ciclosporin: The risk of a nephrotoxic effect by ciclosporin is increased by co administration of certain NSAIDs. Similarly, this effect cannot be excluded for combinations of ciclosporin with ibuprofen.

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

Sulfonylureas: NSAIDs may increase the effects of sulfonylureas. Rare cases of hypoglycaemia were reported in patients with concomitant administration of sulfonylurea and ibuprofen. Monitoring of blood glucose levels is recommended as a precaution during concomitant use of ibuprofen and sulfonylureas.

Aminoglycosides: NSAIDs may reduce the elimination of aminoglycosides.

Tacrolimus: The risk of nephrotoxicity is increased if the two medicinal products are administered concomitantly.

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

Probenecid and sulfinpyrazone: Medicinal products containing probenecid or sulphinpyrazone can delay the excretion of ibuprofen.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions

associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

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

CYP2C9 inhibitors: Concomitant use of ibuprofen and CYP2C9 inhibitors may increase exposure to ibuprofen (a CYP2C9 substrate). In one study with voriconazole and fluconazole (CYP2C9 inhibitors), an 80 - 100% greater exposure to S(+) ibuprofen was shown. A reduction in the ibuprofen dose should be considered when potent CYP2C9 inhibitors are co-administered, especially when high doses of ibuprofen are administered together with either voriconazole or fluconazole.

Gingko biloba: Ginkgo can increase the risk of bleeding with NSAIDs.

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

Alcohol, bisphosphonates and oxpentifylline (pentoxifylline): May potentiate the gastrointestinal adverse reactions and the risk of bleeding and 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 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 embryofoetal 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 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 sections 4.3 and 5.3).

Breast-feeding
Only small amounts of ibuprofen pass into human breast milk. Since harmful effects to infants have not become known to date, interruption of breast-feeding is usually not necessary during short-term treatment with the recommended doses.

Fertility
There is some evidence that medicinal products that 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

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

4.8 Undesirable effects

The list of the following undesirable effects includes all reported adverse reactions during treatment with ibuprofen, including those in rheumatic patients receiving high-dose, long-term therapy. Frequencies beyond very rare reports relate to the short-term use of daily doses up to a maximum 1 200 mg ibuprofen for oral formulations and a maximum of 1,800 mg for suppositories.

It must be remembered that the following adverse drug reactions are mainly dose dependent and vary between individuals.

The most commonly observed adverse reactions are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, may occur, especially in elderly patients (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 use. Less frequently, gastritis has been observed. In particular, the risk of gastrointestinal bleeding is dependent on the dose range and duration of use.

Oedema, hypertension and heart failure have been reported in association with NSAID

treatment.

Clinical studies suggest that the use of ibuprofen, particularly at high doses (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).

Adverse events which have been associated with ibuprofen are given below, listed by system organ class and frequency. Frequencies are defined as: 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). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

System organ class	**Frequency**	**Undesirable effects**
Infections and infestations	Very rare	Exacerbation of infection-related inflammation (e.g. development of necrotising fasciitis) has been described in temporal association with the systemic use of non-steroidal anti-inflammatory drugs. This is possibly associated with the mechanism of action of non-steroidal anti-inflammatory drugs. The patient should be advised to consult a physician immediately, if signs of infection appear or deteriorate during the use of <Invented name>. It should be checked whether there is an indication for anti-infective/antibiotic therapy. The symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or clouding of consciousness have been observed during ibuprofen use. Patients with autoimmune diseases (SLE, mixed connective tissue disease) seem to be predisposed.
Blood and lymphatic system disorders	Very rare	Haematopoietic disorders (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis). Eosinophilia Coagulopathy (changes in coagulation) Aplastic anaemia Haemolytic anaemia Neutropenia First signs may be: fever, sore throat, superficial oral lesions, influenza-like symptoms, severe exhaustion, epistaxis and skin bleeding. The patient should be instructed to discontinue <Invented name> immediately in such cases, to avoid all self-medication with analgesic or antipyretic medicinal products and to consult a physician.
Immune system disorders	Uncommon	Hypersensitivity reactions with skin rashes and pruritus, as well as asthma attacks (sometimes with drop in blood pressure). In this case, the patient should be instructed to inform a physician immediately and stop taking <Invented name>.
	Very rare	Severe general hypersensitivity reactions. These may manifest as: facial oedema, tongue swelling, inner laryngeal swelling with airway constriction, respiratory distress, tachycardia, drop in blood pressure up to life-threatening shock. At the onset of any such manifestations, which may occur even with initial use, immediate medical assistance is required.
Metabolism and nutrition disorders	Very rare	Hypoglycaemia Hyponatraemia
Psychiatric	Very rare	Psychotic reactions

disorders		Hallucinations Confusion Depression Anxiety
Nervous system disorders	Uncommon	Central nervous disorders such as headache, dizziness, insomnia, agitation, irritability or fatigue.
	Not known	Paraesthesiae Optic neuritis
Eye disorders	Uncommon	Visual disturbances. In this case, the patient should be instructed to inform a physician immediately and stop using ibuprofen.
Ear and labyrinth disorders	Rare	Tinnitus, hearing losses
Cardiac disorders	Very rare	Palpitations, heart failure, myocardial infarction.
	Not known	Kounis syndrome
Vascular disorders	Very rare	Hypertension Vasculitis
Respiratory, thoracic and mediastinal disorders	Very rare	Asthma Dyspnoea Bronchospasm
	Not known	Rhinitis
Gastrointestinal disorders	Common	Gastrointestinal complaints such as pyrosis, abdominal pain, nausea, vomiting, flatulence, digestive problems, diarrhoea, constipation and minor gastrointestinal blood loss, which may cause anaemia in exceptional cases.
	Uncommon	Gastrointestinal ulcers, possibly with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), gastritis.
	Very rare	Oesophagitis, pancreatitis, formation of intestinal, diaphragm-like strictures. At the onset of relatively severe epigastric pain, or in the event of melaena or haematemesis, the patient should be instructed to discontinue the medicinal product and consult a physician immediately.
Hepatobiliary disorders	Very rare	Hepatic dysfunction, liver damage, especially during long-term therapy, liver failure, acute hepatitis, jaundice
Skin and subcutaneous tissue disorders	Very rare	Severe cutaneous adverse reactions (SCARs) (including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis), in exceptional cases severe skin infections and soft-tissue complications may occur during a varicella infection alopecia, purpura.

	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalised exanthematous pustulosis (AGEP) Photosensitivity reactions
Renal and urinary disorders	Rare	Renal tissue damage (papillary necrosis), elevated uric acid concentrations in the blood, elevated urea concentration in the blood.
	Very rare	Oedema formation, especially in patients with arterial hypertension or renal impairment; nephrotic syndrome; interstitial nephritis, which can be accompanied by acute renal impairment.
	Not known	Impaired renal function

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.

4.9 Overdose

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

Symptoms
Most patients who have ingested clinically important amount of NSAIDs develop no more than symptoms including nausea, vomiting, epigastric pain, or more rarely, diarrhoea. Nystagmus, blurred vision, tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as vertigo, dizziness, drowsiness, occasionally agitation and disorientation, loss of consciousness or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur. Hypothermia and hyperkalaemia may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Management

The management should be symptomatic, supportive, including the maintenance of a clear airway, monitoring of cardiac and vital signs until stable.
Oral administration of activated charcoal may be considered, if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Bronchodilators should be given for asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that has been shown to be effective by inhibiting prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, oedema 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
On oral application, ibuprofen is partly absorbed from the stomach and then completely absorbed from the small intestine. In the conducted pivotal bioequivalence study peak plasma concentration was reached after 30 min (median T_{max}) after oral administration of the 400 mg strength of the test product under fasting conditions.

Distribution
The plasma-protein binding is approximately 99 %.

Biotransformation
Ibuprofen is metabolised in the liver (hydroxylation, carboxylation, conjugation).

Elimination
The pharmacologically inactive metabolites are completely eliminated, mainly via the renal (90 %), but also biliary. The elimination half-life in healthy individuals and in those with liver and kidney disease is 1.8 to 3.5 hours.

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Crospovidone (type A)
Copovidone
Purified Talc
Magnesium stearate

Tablet coating
Polyvinyl alcohol, part hydrolysed
Titanium dioxide (E171)
Macrogol 4000
Purified talc
Iron oxide red (E172) (<Product name> 200 mg only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

<Product name> 200 mg
[DE/H/6954/001-002/DC]
Opaque PVC/PVDC//Au blisters in boxes of 2, 4, 6, 8, 10, 12, 15, 16, 20, 24 or 30 tablets.
[DE/H/6955/001-002/DC]
Opaque PVC/PVDC//Al blisters in boxes of 10 or 20 tablets.
<Product name> 400 mg

[DE/H/6954/001-002/DC]
Opaque PVC/PVDC//Au blisters in boxes of 10, 12, 20, 24, 30 or 50 tablets.
[DE/H/6955/001-002/DC]
Opaque PVC/PVDC//Al blisters in boxes of 10, 20, 30 or 50 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product poses 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

Healthypharm B.V.
Van de Reijtstraat 31-E
4814 NE Breda
Nederland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 127748 Ibuprofen (als lysine) HTP 200 mg, filmomhulde tabletten
RVG 127750 Ibuprofen (als lysine) HTP 400 mg, filmomhulde tabletten

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 14 juli 2022

10. DATE OF REVISION OF THE TEXT

Laatste wijziging betreft de rubrieken 4.4 en 4.8: 29 februari 2024