# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen Farmalider 200 mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of ibuprofen:

Excipient with known effect:

Each film-coated tablet contains 15 mg of lactose monohydrate.

For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Film-coated tablet

Oblong, biconvex, white-coloured coated tablets with a score line on one side and smooth on the opposite side. The dimensions of the film-coated tablets are 6 mm of width, 12 mm of length and 4.2 mm of thick.

The score line is not intended for breaking the tablet.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Ibuprofen Farmalider is indicated for the short-term symptomatic treatment of mild to moderate pain and / or fever.

Ibuprofen Farmalider is indicated adolescents from 40 kg body weight (12 years of age and above) and adults.

### 4.2 Posology and method of administration

Posology

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

The dosage is in line with the details in the following table.

| **Body weight (Age)** | **Single dose** | **Maximum daily dose** |
|---|---|---|
| ≥ 40 kg (Adults and | 200-400 mg (1-2 tablets) | 1200 mg ibuprofen (6 tablets) |

| | | |
|---|---|---|
| adolescents from 12 years) | | |

The respective dosing interval should be chosen in line with the symptomatology and the maximum daily dose. The interval between doses should not be below 6 hours. The recommended maximum daily dose should not be exceeded.

Paediatric population

Ibuprofen Farmalider is not intended for use in adolescents under 40 kg body weight or children under 12 years of age.

Elderly patients

No special dosage adjustment is required. Due to possible undesirable-effect profile (see section 4.4), it is recommended to monitor the elderly particularly carefully.

Renal insufficiency (see section 5.2):

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

Hepatic insufficiency (see section 5.2):

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

For short-term use only.

If in adolescents from 12 years 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 in the case of fever or for more than 4 days in the treatment of pain, or if symptoms worsen a doctor should be consulted.

Method of administration

For oral use.

The tablets should be swallowed whole with a glass of water.

In patients with a sensitive stomach, it is recommended to take this medicine during meals.

## 4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- history of bronchospasm, asthma, rhinitis, urticaria, angioneurotic oedema or other allergic reactions after having used other non-steroidal anti-inflammatory drugs (NSAIDs).
- history of gastrointestinal haemorrhage or perforation related to previous treatment with NSAIDs.
- active, or history of recurrent peptic ulcer / haemorrhage (two or more distinct episodes of proven ulceration or haemorrhage).
- severe heart failure (NYHA Class IV).

- severe renal or severe hepatic impairment.
- unclarified blood-formation disturbances.
- during the third trimester of pregnancy (see section 4.6.).
- cerebrovascular or other active bleeding.
- severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

## 4.4 Special warnings and precautions for use

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. The elderly are at increased risk of the consequences of adverse reactions.

Ibuprofen should only be used with strict assessment of the benefit/risk ratio:

-Systemic lupus erythematosus as well as those with mixed connective tissue disease – due to increased risk of aseptic meningitis (see Section 4.8).

-Congenital disorders of porphyrin metabolism (e.g. acute intermittent porphyria).

Particularly careful monitoring by a doctor is required:

-Gastrointestinal disorders and chronic inflammatory intestinal disease (ulcerative colitis, Crohn´s disease) (see Section 4.8).

-A history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy (see Section 4.3 and Section 4.8).

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

-Hepatic impairment (see Section 4.3 and Section 4.8).

-Directly after major surgery.

-In dehydration.

-In patients who suffer from hayfever, nasal polyps, chronic swelling of the nasal mucosa or chronic obstructive respiratory disorder as there is an increased risk of allergic reaction occurring. 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.

Respiratory

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

Other NSAIDs

Use with concomitant NSAIDs including cyclo-oxygenase-2 selective inhibitors should be avoided.

Gastrointestinal risks

Gastrointestinal bleeding, ulceration or perforation, which can fatal, have been reported with all. NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses and 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 gastrointestinal toxicity, particularly with elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stage 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 antiplatelet agents 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 these conditions 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 generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8). Most of these reactions occurred within the first month. If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infections complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of ibuprofen in case of varicella.

Cardiovascular and cerebrovascular effects:

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

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

suggest that low dose ibuprofen (e.g. ≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.

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

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

Cases of Kounis syndrome have been reported in patients treated with Ibuprofen Farmalider 200 mg. 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.

Renal effects:

Ibuprofen may cause the retention of sodium, potassium and fluid in patients who have not previously suffered from renal disorders because of its effect on renal perfusion. This may cause oedema or even lead to cardiac insufficiency or hypertension in predisposed patients.

As with other NSAIDs, the prolonged administration of ibuprofen to animals has resulted in renal papillary necrosis and other pathological renal changes. In humans, there have been reports of acute interstitial nephritis with haematuria, proteinuria and occasionally nephrotic syndrome. Cases of renal toxicity have also been observed in patients in whom prostaglandins play a compensatory role in the maintenance of renal perfusion. In these patients, administration of NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of suffering this reaction are those with renal dysfunction, heart failure, hepatic dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID treatment is generally followed by recovery to the pre-treatment state.

In general, the habitual use of analgesics, especially the combination of different analgesic drug substances, can lead to lasting renal lesions with the risk of renal failure (analgesic nephropathy).

Paediatric population

There is a risk of renal impairment in dehydrated adolescents.

Others:

Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of a 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). Patients with coagulation disturbances should therefore be monitored carefully.

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

Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

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.

Regarding female fertility, see section 4.6.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, or glucose- galactose malabsorption should not take this medication.

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Interference with serological testing:

- Bleeding time (may be prolonged for 1 day after discontinuation of treatment).
- Blood glucose concentration (may decrease).
- Creatinine clearance (may decrease).
- Hematocrit or haemoglobin (may decrease).
- Blood urea nitrogen concentrations and serum creatinine and potassium concentrations (may increase).
- With liver function tests: increased transaminase values.

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.

## 4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen (like other NSAIDS) should only be taken with caution with the following medicinal products:

- *Anticoagulants*: NSAIDs may enhance the effect of anticoagulants, such as warfarin (see section 4.4).
- *Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs):* increased risk of gastrointestinal bleeding (see section 4.4).
- *Acetylsalicylic acid:* Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical

situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

- *Corticosteroids:* increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- *Other NSAIDs:* The concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergist effect. The concomitant use of ibuprofen with other NSAIDs should therefore be avoided (see section 4.4).
- *Methotrexate:* NSAIDs inhibit the tubular secretion of methotrexate and certain metabolic interactions may occur resulting in decreased clearance of methotrexate. The administration of Ibuprofen within 24 hours before or after administration of methotrexate may lead to an elevated concentrations of methotrexate and an increase in its toxic effect. Therefore, concomitant use of NSAIDs and high doses of methotrexate should be avoided. Also, the potential risk of interactions in low dose treatment with methotrexate should be considered, especially in patients with impaired renal function. In combined treatment, renal function should be monitored.
- *Mifepristone:* If NSAIDs are used within 8-12 days after the mifepristone administration, they may decrease the effect of mifepristone.
- *Digoxin, phenytoin and lithium:* The concomitant use of ibuprofen with digoxin, phenytoin or lithium preparations may increase serum levels of these medicinal products. A check of serum-digoxin, serum-phenytoin and serum-lithium levels is not as a rule required on correct use (over 3-4 days maximum).
- *Probenecid and sulfinpyrazone:* Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.
- *Quinolone antibiotics:* Animal data indicate that NSAIDs can increase the risk of convulsion 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.
- *Sulphonylureas*: NSAIDs may enhance the effect of sulphonylureas. In the case of simultaneous treatment, monitoring of blood glucose levels is recommeded.
- *Ciclosporin*: the risk of a kidney-damaging effect due to ciclosporin is increased through the concomitant administration of certain non-steroidal anti-inflammatory drugs. This effect also cannot be ruled out for a combination of ciclosporin with ibuprofen.
- *Tacrolimus:* The risk of nephrotoxicity is increased if the two medicinal products are administered concomitantly.
- *Zidovudine*: There is evidence of an increased risk of haemarthrosis and haematomas in HIV positive haemophilia patients who take zidovudine and ibuprofen concomitantly.

- *Aminoglycosides:* NSAIDs can reduce the excretion of aminoglycosides andincrease their toxicity.
- *Herbal extracts:* Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.
- *Diuretics, ACE inhibitors, beta-receptor blocking medicines and angiotensin-II antagonists:* NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. 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 blocking medicines or angiotensin-II antagonists and agents that inhibit cyclooxygenase 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.

  The concomitant administration of ibuprofen and potassium-sparing diuretics may lead to hyperkalaemia.
- *Cholestyramine*: Concomitant treatment with cholestyramine and ibuprofen results in prolonged and reduced (25%) absorption of ibuprofen. The medicinal products should be administered with at least two hours interval.
- *Alcohol:* the use of ibuprofen in individuals with chronic alcohol consumption (14-20 drinks/week or more) should be avoided due to increased risk of significant central nervous system and GI adverse effects, including bleeding .
- *Pentoxifylline:* In patients receiving ibuprofen in combination with pentoxifylline may increase the risk of bleeding, it is recommended to monitor bleeding time.

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*

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

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, 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 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 areis found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors

-may expose the foetus to:

- Cardio-pulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction (see above), which may progress to renal failure with oligohydroamniosis.

-may exposure the mother and the neonate, at the end of the pregnancy, to:

- Possible prolongation of bleeding time, an antiaggregant effect which may occur even at very low doses;
- Inhibition of uterine contractions, resulting in delayed or prolonged labour.

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

*Breastfeeding*

Ibuprofen and its metabolites pass only in low concentrations into breast milk. Since harmful effects to infants have not become known to date, an interruption of breast-feeding is usually not necessary during short-term treatment with ibuprofen at 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 upon withdrawal of treatment.

## 4.7 Effects on ability to drive and use machines

If taken as recommended ibuprofen has generally negligible influence on the ability to drive and use machinery.

As undesirable effects such as tiredness, dizziness and visual disturbances may occur on use of ibuprofen, 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

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

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn’s disease (see section 4.4) have been reported following administration Less frequently, gastritis has been observed. Particularly the risk of gastrointestinal bleeding occurring is dependent on the dose range and the duration of

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

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

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

The following frequencies are taking as a basis when evaluating undesirable effects:

Very common (≥ 1/10),

Common (≥ 1/100, < 1/10),

Uncommon (≥ 1/1000, < 1/100),

Rare (≥ 1/10,000, < 1/1,000),

Very rare (< 1/10,000),

Not known (cannot be estimated from the available data).

Infections and infestations:

Very rare: exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. This is possibly associated with the mechanism of action of the non-steroidal anti-inflammatory drugs.

If signs of an infection occur or get worse during use of ibuprofen, the patient is therefore recommended to go to a doctor without delay. It is to be investigated whether there is an indication for an antiinfective/antibiotic therapy.

Very rare: the symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness clouding has been observed under ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed.

Blood and lymphatic system disorders:

Very rare: disturbances of blood formation (thrombocytopenia, leukopenia, pancytopenia, agranulocytosis or anaemia). The first signs may be fever, sore throat, superficial wounds in the mouth, flu-like symptoms, severe fatigue, nasal and skin bleeding. In such cases, the patient should be advised to discontinue the medicinal product immediately, to avoid any self-medication with analgesics or antipyretics and to consult a physician.

The blood count should be checked regularly in long-term therapy.

Immune system disorders:

Uncommon: hypersensitivity reactions with skin rashes and itching, as well as asthma attacks (possibly with drop in blood pressure). The patient is to be instructed to inform a doctor at once and no longer to take ibuprofen in this case.

Very rare: severe general hypersensitivity reactions. They may present as face oedema, swelling of the tongue, swelling of the internal larynx with constriction of the airways, respiratory distress, racing heart, drop in blood pressure up to life-threatening shock.

If one of these symptoms occurs, which can happen even on first use, the immediate assistance of a doctor is required.

Psychiatric disorders:

Very rare: psychotic reaction, depression.

Nervous system disorders:

Uncommon: central nervous disturbances such as sleeplessness, headache, dizziness, agitation, irritability or tiredness.

Eye disorders:

Uncommon: visual disturbances. In this case, the patient should be instructed to inform the doctor immediately and to discontinue ibuprofen.

Rare: reversible toxic amblyopia.

Ear and labyrinth disorders:

Rare: tinnitus, hearing disorders.

Cardiac disorders:

Very rare: palpitation, heart failure, myocardial infarction

Not known: Kounis syndrome

Vascular disorders

Very rare: arterial hypertension

Gastrointestinal disorders:

Common: gastrointestinal complaints such as pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation and slight gastro-intestinal blood losses that may cause anaemia in exceptional cases.

Uncommon: gastrointestinal ulcers, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), gastritis.

Very rare: oesophagitis, pancreatitis, formation of intestinal, diaphragm-like strictures.

The patient is to be instructed to withdraw the medicinal product and to go to a doctor immediately if relatively severe pain in the upper abdomen or melaena or haematemesis occurs.

Hepatobiliary disorders

Very rare: hepatic damage, particularly in long-term therapy, hepatic dysfunction, hepatic failure, acute hepatitis and jaundice.

Skin and subcutaneous tissue disorders:

Uncommon: skin rash, urticaria, pruritus, purpura (including allergic purpura).

Very rare: Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis), alopecia, photosensitivity reactions and allergic vasculitis. In exceptional cases, severe skin infections and soft tissue complications in varicella infection.

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis (AGEP).

Photosensitivity reactions.

Metabolism and Nutrition Disorders

Not known: Hypokalaemia*

Renal and urinary disorders:

Rare: renal tissue damage (papillary necrosis), particularly in long-term therapy, increased serum uric acid concentration in the blood, increased urea concentration in the blood.

Very rare: reduced urinary excretion and formation of oedemas, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis that may be accompanied by acute renal insufficiency.

Renal function should therefore be checked regularly.

Not known: Renal tubular acidosis*

*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.

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 Yellow Card Scheme:

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

## 4.9 Overdose

*Symptoms*

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely, diarrhoea. Tinnitus, headache, dizziness, vertigo and gastrointestinal bleeding may also occur. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. Children may also develop myoclonic cramps. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to the actions of circulating clotting factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

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

In serious poisoning metabolic acidosis may occur.

*Treatment*

Patient should immediately be transferred to a hospital.

Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Gastric emptying or oral administration of activated charcoal is indicated if the patient presents within one hour of the ingestion of more than 400 mg per kg of body weight. If the ibuprofen has already been absorbed, alkaline substances should be administered to promote the excretion of the acid ibuprofen in the urine. If frequent or prolonged, convulsions

should be treated with intravenous diazepam or lorazepam. Other measures may be indicated by the patient's clinical condition. Bronchodilators should be given for asthma. No specific antidote is available.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

Renal and liver function should be closely monitored.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroids, propionic acid derivates, ATC code: M01AE01

Ibuprofen is a non-steroidal anti-inflammatory drug that, in conventional animal-experiment inflammation models, has proven to be effective, probably through prostaglandin synthesis inhibition. In humans, ibuprofen has an antipyretic effect, reduces inflammatory-related pain and swelling. Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

## 5.2 Pharmacokinetic properties

Absorption:

Ibuprofen administered orally is absorbed quickly with approximately 80% in the gastrointestinal tract. Maximum plasma concentrations are reached (T-max) 1-2 hours after administration.

The administration of ibuprofen together with food delays the Tmax (from ± 2 h fasted to ± 3 h after eating), although this has no effect on the magnitude of absorption.

Distribution:

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

Biotransformation:

Ibuprofen is rapidly metabolised in the liver by hydroxylation and carboxylation of the isobutyl group through CYP2C9 and CYP2C8, to two primary inactive. These

together with unmetabolized ibuprofen, are excreted by the kidney either as such or as conjugates.

Elimination:

Ibuprofen is excreted by the kidney and is complete 24 hours after the last dose. Approximately 10% is eliminated unaltered and 90% is eliminated as inactive metabolites, mainly as glucuronides.

Special populations

*Elderly*

Given that no renal impairment exists, there are only small, clinically insignificant differences in the pharmacokinetic profile and urinary excretion between young and elderly.

*Children*

The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5 mg/kg to 10 mg/kg bodyweight) in children aged 1 year or over, appears similar to that in adults.

*Renal impairment*

For patients with mild renal impairment increased unbound (S)-ibuprofen, higher AUC values for (S)- ibuprofen and increased enantiomeric AUC (S/R) ratios as compared with healthy controls have been reported.

In end-stage renal disease patients receiving dialysis the mean free fraction of ibuprofen was about 3% compared with about1% in healthy volunteers. Severe impairment of renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis (see sections 4.2, 4.3 and 4.4).

*Hepatic impairment*

Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters.

In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) treated with racemic ibuprofen an average 2-fold prolongation of the half-life was observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of (R)-ibuprofen to the active (S)-enantiomer (see sections 4.2, 4.3 and 4.4).

## 5.3 Preclinical safety data

The sub chronic and chronic toxicity of ibuprofen in animal trials showed up mainly in the form of lesions and ulcers 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 an inhibition of ovulation in rabbits and impaired implantation 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.

The active substance ibuprofen may show an environmental risk for the aquatic environment, especially to fish.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Core

Hypromellose

Croscarmellose sodium

Lactose monohydrate

Microcrystalline cellulose

Pregelatinized maize starch

Colloidal anhydrous silica

Magnesium stearate

Coating

Hypromellose

Titanium dioxide (E-171)

Talc

Propylene glycol (E-1520)

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

36 months

## 6.4 Special precautions for storage

Do not store above 25ºC

## 6.5 Nature and contents of container

PVC/PVDC/aluminium blisters in packs of 20 film-coated tablets.

## 6.6 Special precautions for disposal

Not special requirements

## 7 MARKETING AUTHORISATION HOLDER

FARMALIDER, S.A.

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