SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen 400 mg capsules, soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 400 mg Ibuprofen.

Excipient with known effect (per capsule):
96 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

A clear oval transparent soft gelatin capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ibuprofen 400 mg capsules, soft is indicated in adults and adolescents from ≥40 kg (12 years of age and above) for the symptomatic relief of mild to moderate pain such as headache, acute migraine headaches with or without aura, muscular pain, period pain/dysmenorrhoea, feverishness and pain associated with a common cold

4.2 Posology and method of administration

For oral use.

For short-term use only.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).
Adults: If the medicinal product is required for more than 4 days for pain or 3 days for fever and migraine headaches or if the symptoms worsen, the patient should consult a doctor.

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

If people experience mild indigestion it is recommended to take this medicine with food or milk to avoid gastrointestinal problems.

Adults and adolescents from ≥40 kg in weight (12 years of age and above):
400 mg (one capsule) with water.

400 mg (one capsule) to be repeated, if necessary, with intervals of at least 6 hours.
Do not take more than 1200 mg ibuprofen (three capsules) in any 24 hour period.

Special patient groups
The elderly and patients with renal and hepatic impairment should always start treatment with the lowest effective dose.

Paediatric population:
Ibuprofen 400 mg capsule, soft is contraindicated in adolescents under 40 kg body weight and in children, see section 4.3.

Elderly:
No special dose adjustment is required. Because of the possible undesirable-effect profile (see section 4.4), it is recommended to monitor the elderly particularly carefully.

Renal insufficiency:
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 dysfunction, see section 4.3).

4.3 Contraindications

Hypersensitivity to ibuprofen, peanut or soya, or to any of the excipients listed in section 6.1.

Patients who have previously shown hypersensitivity reactions (e.g. bronchospasms, asthma, rhinitis, angioedema or urticaria) in response to acetylsalicylic acid or other NSAIDs.

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Bleeding diathesis or coagulation disorders.

Patients with severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV) (see section 4.4).

Patients with cerebrovascular or other active bleeding.

Use with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors (see section 4.5).

Patients with unclarified blood-formation disturbances.

Patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

We do not recommend taking Ibuprofen 400 mg Capsule, Soft if you are pregnant.

Adolescents under 40 kg body weight and children.

4.4 Special warnings and precautions for use

Caution is required in patients with certain conditions:

- systemic lupus erythematosus as well as those with mixed connective tissue disease, due to increased risk of aseptic meningitis (see section 4.8).
- congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria).
- gastrointestinal disorders and chronic inflammatory intestinal disease as these conditions may be exacerbated (ulcerative colitis, Crohn's disease) (see section 4.8).
- oedema, hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur (see section 4.5).
- renal impairment as renal function may further deteriorate (see section 4.3 and 4.8).
- hepatic dysfunction (see section 4.3 and 4.8).
- directly after major surgery.
- in patients who react allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of Ibuprofen (see section 4.3).
- in patients who suffer from hayfever, 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 (see section 4.3).
- bronchial asthma (see section 4.3 and 4.8).
  Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease (see section 4.6).
- 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 on withdrawal of treatment.

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).

There is a risk of renal impairment in dehydrated adolescents.

Gastrointestinal effects

The use of Ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

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 and perforation:
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI 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 agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

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

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

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 (see also section 4.7).

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 high doses (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. 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.

Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reactions 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 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 use of Ibuprofen in case of varicella (see section 4.8).
Masking of symptoms of underlying infections
Ibuprofen 400 mg Soft Capsules 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.
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.

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.

In general terms, the habitual intake of painkillers, particularly on combination of several pain-relieving active substances, may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore it should be avoided.

The use of NSAIDs may mask the symptoms of infection.

This medicinal product contains 57.6mg sorbitol (E420) in each capsule. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should not be used in combination with:

- Acetylsalicylic acid (above 75 mg daily): as this may increase the risk of adverse reactions (see section 4.3).

- Other NSAIDs, including cyclo-oxygenase-2 inhibitors: as these may increase the risk of adverse reactions (see section 4.3 and 4.4).

Ibuprofen should be used with caution 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 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).

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

- Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

- Diuretics, ACE inhibitors, betareceptor-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 an ACE inhibitor, betareceptor-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.

  In particular, concomitant use of potassium-sparing diuretics may increase the risk of hyperkalaemia.

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

- Lithium, digoxin and phenytoin: there is evidence for potential increase in plasma levels of these medicinal products when co-administered with ibuprofen. If used correctly (maximum dose for adults for 4 days),

monitoring of the plasma concentrations of lithium, digoxin or phenytoin is usually not needed.

- Probenecid and sulfinpyrazon: medicinal products that contain probenecid or sulfinpyrazon may delay the excretion of ibuprofen.

- Methotrexate: the administration of Ibuprofen 400 mg capsule, soft within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase of its toxic effect.

- Cyclosporin: inhibition of renal prostaglandin activity by NSAIDs may increase the plasma concentration of cyclosporin and the risk of cyclosporin-induced nephrotoxicity.

- Tacrolimus: the risk of nephrotoxicity is increased if ibuprofen and tacrolimus are co-administered.

- Zidovudine: there is evidence of an increased risk of haemarthroses and haematoma in HIV positive haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

- Sulphonylureas: there is evidence of interactions between NSAIDs and antidiabetic medicinal products (sulphonylureas). Although no specific interactions between ibuprofen and sulphonylureas have been described, blood glucose values should be monitored as a precaution during co-administration of ibuprofen and sulphonylureas.

- 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: Concomitant treatment with cholestyramine and ibuprofen results in prolonged and reduced (25%) absorption of ibuprofen. The medicinal products should be administered with at least one hour interval.

- Aminoglycosides: NSAIDs can slow down the elimination of aminoglycosides and increase their toxicity.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy:
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.
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, to minimize any risks, we do not recommend taking Ibuprofen 400 mg Capsules, Soft during any trimester of pregnancy..
If ibuprofen is used by a woman attempting to conceive, or during the first and second trimesters 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.

Therefore, to minimize any risks, we do not recommend taking Ibuprofen 400 mg Liquid Capsules, Soft during any trimester of pregnancy.

Breastfeeding:
In limited studies Ibuprofen and its metabolites appear in breast milk in very low concentrations. Since no harmful effects to infants are known to date, it is usually not necessary to interrupt breast-feeding during short-term use of Ibuprofen at the recommended doses.
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

Patients who experience dizziness, drowsiness, vertigo or visual disturbances while they are taking ibuprofen, should avoid driving or using machinery. This remark applies to a greater extent in combination with alcohol (see section 4.4). Single administration or short term use of ibuprofen does not usually warrant the adoption of any special precautions.

4.8 Undesirable effects

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 most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.
Oedema, hypertension, and cardiac failure have been reported in association with NSAID treatment.
Hypersensitivity reactions have been reported and these may consist of:

a. Anaphylaxis and non-specific allergic reactions,
b. Respiratory tract reactivity comprising bronchospasm, asthma, aggravated asthma, or dyspnoea,
c. Various skin reactions, e.g. rarely, exfoliative and bullous dermatoses (including toxic epidermal necrolysis and erythema multiforme), angioedema, pruritus and urticaria.

Adverse reactions have been ranked under headings of frequency using the following convention: 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)); not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Adverse Events	Frequency
Infections and infestations	Exacerbation of infection-related inflammations (e.g. development of necrotizing fasciitis) coinciding with the use of nonsteroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the nonsteroidal anti-inflammatory drugs. If 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 anti-infective/antibiotic therapy. The symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness clouding have been observed under Ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed.	Very rare
Blood and Lymphatic System Disorders	Disturbances to blood formation (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranuloctosis, aplastic anaemia, haematolytic anaemia). The first signs may be fever, sore throat, superficial wounds in the mouth, influenza-like complaints, severe lassitude, nosebleeds and skin bleeding. In such cases the patient should be advised to discontinue the medicine 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.	Very rare
Immune System Disorders	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.	Uncommon
	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.	Very rare

Psychiatric disorders	Psychotic reactions, depression, nervousness	Very rare
Nervous System Disorders	Central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness	Uncommon
Eye disorders	Visual disturbances	Uncommon
Ear and labyrinth disorders	Tinnitus	Rare
Cardiac Disorders	Palpitations, heart failure, myocardial infarction	Very rare
	Kounis Syndrome	Not known
Vascular disorders	Arterial hypertension	Very rare
Respiratory, thoracic and mediastinal disorders	Asthma, bronchospasm,dyspnoea and wheezing	Very rare
Gastrointestinal Disorders	Gastro-intestinal complaints such as dyspepsia, pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation and slight gastro-intestinal blood losses that may cause anaemia in exceptional cases.	Common
	Gastrointestinal ulcers, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), gastritis	Uncommon
	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 severe pain in the upper abdomen or melaena or haematemesis occurs.	Very rare
Hepatobiliary Disorders	Hepatic dysfunction, hepatic damage, particularly in long-term therapy, hepatic failure, acute hepatitis	Very rare
Skin and Subcutaneous Tissue Disorders	Various skin rashes	Uncommon
	Severe cutaneous adverse reactions (SCARs) (including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)). In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations").	Very rare
	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Acute generalised exanthematous pustulosis (AGEP). Photosensitivity reactions.	Not known

Renal and Urinary Disorders	Kidney-tissue damage (papillary necrosis) and elevated uric acid concentrations in the blood may also occur rarely.	Rare
	Renal and urinary disorders	Very rare
	Ureteric colic, dysuria	Not known
	Renal tubular acidosis*	Not known
	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.	Very rare
Investigations	Decreased haematocrit and haemoglobin levels.	Very rare
Metabolism and Nutrition Disorders	Decreased Appetite	Not known
	Hypokalaemia*	Not known

*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.

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).

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 at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

In adolescents and adults, the dose response effect is not clear cut. The half-life in overdose is 1.5 – 3 hours.

In serious poisoning metabolic acidosis may occur.

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 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 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. 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). Exacerbation of asthma is possible in asthmatics.

Management

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal 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. Give bronchodilators 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.

Ibuprofen is a phenylpropionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever.

Furthermore, ibuprofen reversibly inhibits 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 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

Ibuprofen is rapidly absorbed from the gastro-intestinal tract, peak serum concentrations occurring 1-2 hours after administration of conventional film-coated tablets ibuprofen. However, ibuprofen is more rapidly absorbed from the gastrointestinal tract following the administration of Ibuprofen 400 mg capsule, soft, with peak plasma concentrations occurring approximately 46 minutes after administration in the fasting state.

When taken with food, peak levels are observed after 1-2 hours with conventional film-coated tablets.

Ibuprofen protein binding is approximately 99%. After an oral dose, ibuprofen is 75–85% excreted via kidneys during the first 24 hours (mainly in the form of two metabolites), the remainder being eliminated in the faeces following excretion in bile. Excretion is complete within 24 hours.

The half-life of ibuprofen is about 2 hours.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

5.3 Preclinical safety data

The sub chronic and chronic toxicity of ibuprofen in animal experiments consisted mainly of lesions and ulcerations in the gastro-intestinal tract.
In-vitro and *in-vivo* investigations have produced no clinically relevant evidence of ibuprofen having mutagenic effects. 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 rats and rabbits have shown that ibuprofen crosses the placenta. Following administration of maternotoxic doses, an increased rate of malformations (ventricular septal defects) occurred in the progeny of rats.
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.
In animal studies it has been observed that the use of NSAIDs, known to inhibit prostaglandin synthesis, may increase the incidence of dystocia and delayed parturition.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Macrogol 600
Potassium hydroxide
Purified water

Capsule shell
Gelatin
Sorbitol Liquid, Partially Dehydrated (420)
May contain trace amount of Medium Chain Triglycerides and Lecithin (soya bean).

Capsule printing
Opacode WB black NS-78-17821 *
*The ink contains: Black iron oxide, HPMC 2910/Hypromellose 6cP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blisters formed of PVC/PE/PVdC/Al packed into cartons and PVC/PE/PVdC/Al/PET packed into cartons.

Each carton may contain 4, 10, 12, 15, 16, 20 or 30 capsules in blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

75Pharma Limited

123 Buckingham Palace Road

SW1W 9SH London

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 54677/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/11/2011

10 DATE OF REVISION OF THE TEXT

04/10/2024