SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen <TRADE NAME> <STRENGTH> capsules

<REGARDING THE APPROVAL>

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsules contains Ibuprofen <STRENGTH>

For the full list of excipients, see section 6.1.

<REGARDING THE APPROVAL>

1. PHARMACEUTICAL FORM

Capsules <REGARDING THE APPROVAL>

1. CLINICAL PARTICULARS
   1. Therapeutic indications

For the relief of migraine-headaches, backache, dental pain, neuralgia and period pains as well as rheumatic and muscular pains.

Ibuprofen relieves pain and reduces inflammation and temperature as well as relieving headaches and other types of pain. It also relieves cold and flu symptoms.

* 1. Posology and method of administration

For short-term use only.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

Adults and adolescents weighing from 40 kg (12 years of age and above). Take one tablet with water, up to 3 times a day.

Leave at least 4 hours between doses and do not take more than 3 tablets in any 24 hour period.

If in children and adolescents between 12 and 18 years this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted. Adults should consult a doctor if symptoms persist or worsen, or if the product is required for more than 10 days.

Not for use by children under 12 years of age.

**Special patient groups**

Elderly:

No special dose adjustment is required. Because of the possible undesirable-effect profile (see section 4.4), the elderly should be monitored 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).

**Method of administration**

For oral administration

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

* 1. Contraindications

Hypersensitivity to ibuprofen or any of the excipients in the product.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, or urticaria) in response to aspirin or other non-steroidal anti-inflammatory drugs.

Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Severe heart failure (NYHA ClassIV), renal failure or hepatic failure (see section 4.4)

Last trimester of pregnancy (see section 4.6)

* 1. Special warnings and precautions for use

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

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

**Respiratory**:

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

**Other NSAIDs**:

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

**SLE and mixed connective tissue disease**:

Systemic lupus erythematosus as well as those with mixed connective tissue disease – increased risk of aseptic meningitis (see section 4.8)

**Renal**:

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

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

**Hepatic**:

Hepatic dysfunction (see sections 4.3 and 4.8)

**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.

**Gastrointestinal**:

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

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

Patients with a history of GI toxicity, particularly the 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 aspirin (see section 4.5).

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

**Severe skin reactions**:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Ibuprofen should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

**Masking of symptoms of underlying infections**:

This medicinal product 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 this medicine is administered for pain or fever in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

**Excipient information**

<REGARDING THE APPROVAL>

* 1. Interaction with other medicinal products and other forms of interaction

**Aspirin (Acetylsalicylic Acid)**: Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects unless low-dose aspirin (not above 75mg daily) has been advised by a doctor (see Section 4.4).

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin (acetylsalicylic acid) on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

**Other NSAIDs including cyclooxygenase-2 selective inhibitors**: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4)

**Ibuprofen should be used with caution in combination wit**h:

**Corticosteroids**: as these may increase the risk of gastrointestinal ulceration or bleeding (see Section 4.4)

**Antihypertensives and diuretics**: since NSAIDs may diminish the effects of these 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 or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or angiotensin II antagonists. 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.

**Anticoagulants**: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4).

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

**Cardiac glycosides**: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

**Lithium**: There is evidence for potential increase in plasma levels of lithium.

**Methotrexate**: There is evidence for the potential increase in plasma levels of methotrexate.

**Ciclosporin**: Increased risk of nephrotoxicity.

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

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

**Zidovudine**: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and 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.

* 1. Fertility, pregnancy and lactation

**Pregnancy**

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The 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, 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 ductusarteriosus and pulmonary hypertension);

- renal dysfunction (see above), which may progress to renal failure with oligo-hydroamniosis;

• the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;

- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy.

**Breast-feeding**

Ibuprofen and its metabolites can pass in low concentrations into the breast milk. No harmful effects to infants are known to date, so for short-term treatment with the recommended dose for pain and fever interruption of breast-feeding would generally not be necessary.

**Fertility**

There is some evidence that drugs which inhibit cyclo-oxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment (see section 4.4).

* 1. 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. Single administration or short term use of ibuprofen does not usually warrant the adoption of any special precautions. This applies to a greater extent in combination with alcohol.

* 1. 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. 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 NSAID treatment.

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).

Hypersensitivity reactions have been reported and these may consist of:

(a) non-specific allergic reactions and anaphylaxis

(b) respiratory tract reactivity, e.g. asthma, aggravated asthma, bronchospasm, dyspnoea

(c) various skin reactions, e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme)

The patient is to be instructed to inform a doctor at once and to stop taking Ibuprofen Express if they experience any of the above.

Please note that within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. using the following convention: common (≥ 1/100, < 1/10); uncommon (≥1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), Not know (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 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.

**Blood and Lymphatic System Disorders**:

Very rare: Disturbances to blood formation (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranuloctosis). 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

**Immune system disorders (Hypersensitivity)**:

Uncommon: Hypersensitivity reactions with urticaria and pruritus, as well as asthma attacks (possibly with drop in blood pressure).

Very rare: severe general hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock). Exacerbation of asthma and bronchospasm.

**Psychiatric disorders**:

Very rare: Psychotic reactions, depression

**Nervous System Disorders**:

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

**Eye disorders**:

Uncommon: Visual disturbances

**Ear and labyrinth disorders**:

Rare: Tinnitus, Hearing impaired

**Cardiac Disorders**:

Very rare: palpitations, heart failure, myocardial infarction

**Vascular disorders**:

Very rare: Arterial hypertension, Vasculitis

**Gastrointestinal Disorders**:

Common: 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

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 severe pain in the upper abdomen or melaena or haematemesis occurs.

**Hepatobiliary Disorders**:

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

**Skin and Subcutaneous Tissue Disorders**:

Uncommon: Various skin rashes

Very rare: Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell’s syndrome), alopecia. In exceptional cases, severe skin infections and softtissue complications may occur during a varicella infection (see also "Infections and infestations").

Not Known: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Acute generalised exanthematous pustulosis (AGEP). Photosensitivity reactions.

**Renal and Urinary Disorders**:

Rare: Kidney-tissue damage (papillary necrosis) and elevated uric acid concentrations in the blood may also occur rarely. Elevated urea concentrations in the blood.

Very rare: 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.

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 Health Product Vigilance Center; HPVC.

* 1. Overdose

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

**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. 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. No special antidote is available.

1. PHARMACOLOGICAL PROPERTIES
   1. Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivative

ATC Code: M01A E01

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that in the conventional animal-experiment inflammation models has proven to be effective via prostaglandin-synthesis inhibition. In humans, ibuprofen reduces inflammatory-related pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits ADP – and collagen – induced platelet aggregation

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81mg), 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).

* 1. Pharmacokinetic properties

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

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

Peak plasma levels following oral administration of a normal-release pharmaceutical form (tablet) are reached after 1 - 2 hours. Ibuprofen is absorbed rapidly from the gastrointestinal tract following oral administration. In a pharmacokinetic study (R07-1009), the time to peak plasma levels (median Tmax) in fasted state, for normal release pharmaceutical form ibuprofen acid tablets (Ibuprofen tablets) was 90 min compared with 40 min for Ibuprofen Capsules, soft. Ibuprofen is detected in the plasma for more than 8 hours after administration of Ibuprofen .

* 1. Preclinical safety data

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

1. PHARMACEUTICAL PARTICULARS
   1. List of excipients

<REGARDING THE APPROVAL>

* 1. Incompatibilities

Not Applicable

* 1. Shelf life

<REGARDING THE APPROVAL>

* 1. Special precautions for storage

<REGARDING THE APPROVAL>

* 1. Nature and contents of container

<REGARDING THE APPROVAL>

* 1. Special precautions for disposal

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION HOLDER

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION NUMBER(S)

<REGARDING THE APPROVAL>

1. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<REGARDING THE APPROVAL>

1. DATE OF REVISION OF THE TEXT1

<REGARDING THE APPROVAL>