SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen 200 mg Caplets

Ibuprofen 200 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg of Ibuprofen.

Excipients with known effect:
Each tablet contains: 92.80 mg sucrose and 123 mg lactose
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Coated tablet
(tablet).

White capsule shaped sugar coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the relief of period pains as well as rheumatic or muscular pain, pain of non serious arthritic conditions back ache, neuralgia, migraine, headache, dental pain, dysmenorrhoea. 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.

4.2 Posology and method of administration

For oral administration and short term use only. The tablets should be swallowed whole with a drink of water.

Adults, the elderly and children over 12years: Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Adults and the elderly: If this medicinal product is required for more than 10 days, or if symptoms persist or worsen, consult your doctor.

Adolescents: If this medicinal product is required for more than 3 days, or if symptoms persist or worsen, consult your doctor.

200mg-400mg (1-2 tablets) to be taken up to 3 times a day as required.

Leave at least four hours between doses and do not take more than 1200mg (6 caplets) in any 24 hour period.

Children under 12 years of age: Not recommended.

4.3 Contraindications

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

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, relating to previous NSAIDs therapy.
Ibuprofen should not be given to patients with conditions involving an increased tendency to bleeding.

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

Last trimester of pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

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

As with other NSAIDs, ibuprofen may mask the signs of infection.

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 due to the increased risk of ulceration or bleeding and other side effects. (see section 4.5).

SLE and mixed connective tissue disease: Systemic lupus erythematosus (SLE) and mixed connective tissue disorders- increased risk of aseptic meningitis (see section 4.8)

Aseptic meningitis: Aseptic meningitis has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Renal: Renal impairment as renal function may further deteriorate. Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration.

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, the administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and ACE inhibitors and the elderly. Renal function should be monitored in these patients (see section 4.3 and 4.8). Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

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 mild to moderate 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 (2400mg/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. ≤1200mg/day) is associated with an increased risk of myocardial infarction.

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.

Careful consideration should also be exercised before initiating longer-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.

Haematological effects: Ibuprofen, like other NSAIDs, can interfere with platelet aggregation and has been shown to prolong bleeding time in normal subjects.

Impaired female fertility: There is limited evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. The use of ibuprofen therefore, may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered. This is reversible upon withdrawal of treatment.

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

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

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of 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 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 aspirin (see section 4.5).

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

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

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

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

The label will include:
Read the enclosed leaflet before taking this product.
Do not use if you:

- have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding
- are allergic to Ibuprofen or any other ingredient of the product, aspirin or other related painkillers
- are taking other NSAID painkillers, or aspirin with a daily dose above 75mg

Speak to a pharmacist or your doctor before taking if you:

- have or have had asthma, diabetes, high cholesterol, high blood pressure, a stroke, heart, liver, kidney or bowel problems
- are a smoker
- are pregnant

If symptoms persist or worsen, or if new symptoms occur, consult your doctor or pharmacist.

4.5 Interactions with other medicines and other forms of interactions

Ibuprofen should be avoided in combination with:
Acetylsalicylic acid: Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.
Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective 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 with:
Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4)
Antihypertensive, beta-blockers and diuretics: NSAIDs may diminish the effect 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, periodically thereafter. Diuretics can increase the risk of nephrotoxicty of NSAIDs.

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

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

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

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

Lithium: There is evidence for potential increases in plasma levels of lithium due to decreased elimination of lithium.

Methotrexate: There is a potential for an increased in plasma methotrexate as NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance 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.
A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs. Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy.

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

Zidovudine: Increased risk of haemoatological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of 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.

Sulfonylureas: NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides.

Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

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.

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. 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.

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

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, 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.

Lactation
In limited studies, Ibuprofen appears in breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

None expected at recommended doses and duration of therapy.

4.8 Undesirable effects

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) various skin reactions, e.g. pruritus,

urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme)
The following list of adverse effects relates to those experienced with ibuprofen at OTC doses, for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Immune System disorders:
Uncommon: hypersensitivity reactions with urticaria and pruritus

Very rare: In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see section 4.4), severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock)

Exacerbation of asthma and bronchospasm

Blood and lymphatic system disorders:
Very rare: Haematopoietic disorders (anaemia, hemolytic anaemia, aplastic anaemia leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained nose and skin bleeding and bruising.

Skin and subcutaneous tissue disorders:
Uncommon: various skin rashes

Very rare: severe forms of skin reactions such as bullous reactions, including Stevens Johnson syndrome, erythema multiforme and toxic epidermal necrolysis, fixed drug eruptions (unknown frequency) can occur.

Nervous system disorders:
Uncommon: Headache
Very rare: Aseptic Meningitis

Cardiac disorders: cardiac failure, angina pectoris
Vascular Disorders
Very rare: Hypertension

Respiratory, thoracic and mediastinal disorders
Very rare: Asthma, bronchospasm, dyspnoea and wheezing

Gastrointestinal disorders:
Uncommon: Abdominal pain, abdominal distension, nausea and dyspepsia
Rare: Diarrhoea, flatulence, constipation, vomiting

Very rare: Peptic ulcer, perforation or gastrointestinal haemorrhage, malaena, haematemesis, sometimes fatal, particularly in the elderly. Exacerbation of ulcerative colitis and Crohn's disease (see section 4.4). Mouth ulceration.

Hepatobiliary disorders:
Very rare: liver disorders, especially in long term treatment hepatitis and jaundice

Renal and urinary disorders:
Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema. Haematuria, interstitial nephritis, nephrotic syndrome, proteinuria

Eye disorders:
Very rare: Visual disturbance

Ear and labyrinth disorders:
Very rare: tinnitus and vertigo

Psychiatric disorders:
Very rare: Nervousness

General disorders and administration site conditions:
Very rare: Oedema, peripheral oedema

Investigations:
Very rare: Decreased haematocrit and haemoglobin levels

Clinical studies suggest that use of ibuprofen particularly at a high dose (2400mg/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 authorization 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.uk/yellowcard

4.9 Overdose

Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults. However, supportive care may be needed in some cases.In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, abdominal pain, lethargy or more rarely diarrhoea within 4 to 6 hours. Tinnitus, dizziness, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation, loss of consciousness or coma. Cardiovascular toxicity, including hypotension, bradycardia and tachycardia have been reported. Occasionally patients develop convulsions. Nystagmus, hypothermia, apnoea, and depression of the CNS and respiratory system have also been rarely reported. 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. In cases of significant overdose, 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.

Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma. Other measures may be indicated by the patient's clinical condition.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

M01A E, Anti-inflammatory and anti-rheumatic products, non-steroids, Propionic acid derivatives.

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy be inhibition of prostaglandin synthesis. In humans ibuprofen reduces

inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Clinical evidence demonstrates that when 400 mg of ibuprofen is taken the pain relieving effects can last for up to 8 hours.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin 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

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys. Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after 1 to 2 hours. These times may vary with different dosage forms.

Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete.

The elimination half life of ibuprofen is approximately 2 hours.

No significant differences in pharmacokinetic profile are observed in the elderly.
In limited studies ibuprofen appears in the breast milk in very low concentrations.

5.3. Preclinical safety data

No data of relevance which is additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Potato Starch
Methylcellulose
Sodium Starch Glycolate
Colloidal Anhydrous Silica
Magnesium Stearate
Sucrose
Talc
Titanium Dioxide (E171)
Maize Starch
Pregelatinised *Maize* Starch

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

5 years.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

Al/PVC blister strips enclosed in an outer carton containing 24, 48 or 96 caplets.

6.6. Instruction for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road
Berkhamsted
Hertfordshire
HP4 1EG
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 17907/0078

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

21st July 2005

10 DATE OF REVISION OF THE TEXT

10/02/2016