SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen Tablets BP 600 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 600 mg of Ibuprofen.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet

Pink coloured capsule shaped film coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ibuprofen is indicated for its analgesic and anti-inflammatory effects in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, osteoarthritis and other non-rheumatoid (seronegative) arthropathies.

In the treatment of non-articular rheumatic conditions, Ibuprofen is indicated in periarticular conditions such as frozen shoulder (capsulitis), bursitis, tendinitis, tenosynovitis and low back pain; Ibuprofen can also be used in soft tissue injuries such as sprains and strains.

Ibuprofen is also indicated for its analgesic effect in the relief of mild to moderate pain such as dysmenorrhoea, dental and post-operative pain and for symptomatic relief of headache, including migraine headache.

4.2 Posology and method of administration

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

Adults: The recommended dosage of Ibuprofen is 1200-1800mg daily in divided doses. Some patients can be maintained on 600-1200mg daily. In severe or acute conditions, it can be advantageous to increase the dosage until the acute phase is brought under control, provided that the total daily dose does not exceed 2400mg in divided doses.

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If NSAIDs are considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should

be monitored regularly for GI bleeding during NSAID therapy. If renal or hepatic function is impaired, dosage should be assessed individually.

Children: The daily dosage of Ibuprofen is 20mg/kg of body weight in divided doses.

In Juvenile Rheumatoid Arthritis, up to 40mg/kg of body weight daily in divided doses may be taken.

Not recommended for children weighing less than 7kg.

For oral administration. To be taken preferably with or after food, with a glass of water. Ibuprofen tablets should be swallowed whole and not chewed, broken, crushed or sucked on to avoid oral discomfort and throat irritation.

4.3 Contraindications

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

Ibuprofen should not be used in patients with active, or history of recurrent Peptic ulcer/ gastrointestinal haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

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

Ibuprofen should not be given to patients with conditions involving an increased tendency to bleeding.

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

During the last trimester of pregnancy (see section 4.6).

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

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 section 4.2, and GI and cardiovascular risks below).

Other NSAIDs:

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

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).

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).

Respiratory disorders: Caution is required if administered to patients suffering from, or with a previous history of bronchial asthma, since NSAIDs have been reported to cause bronchospasm in such patients.

Cardiovascular, Renal and Hepatic Impairment: 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 the elderly. Renal function should be monitored in these patients (see section 4.3).

Ibuprofen should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with ibuprofen administration.

Cardiovascular and cerebrovascular effects: Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention 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 arterial thrombotic events, particularly 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, and smoking) particularly if high doses of ibuprofen (2400mg/day) are required.

Gastrointestinal bleeding, ulceration and perforation: 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. 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 section 4.5)

Patients with a history of gastrointestinal disease, 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.

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)

Renal effects

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, administration of an NSAID may cause a dose-dependant reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

SLE and mixed connective tissue disease: In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8)

Dermatological Effects: 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.

Haematological effects:

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

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.

Impaired female fertility: The use of Ibuprofen 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients.

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin,Cox-2 inhibitors) as this may increase the risk of adverse effects (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).

Anti-hypertensives, beta blockers and diuretics: Reduced anti-hypertensive effect of ACE inhibitors, beta-blockers and diuretics.

Diuretics: Reduced diuretics effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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: Decreased elimination of lithium

Methotrexate: NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate

Ciclosporin: Increased risk of nephrotoxicity.

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.

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

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

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

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.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):

Increased risk of gastrointestinal bleeding with NSAIDs (see section 4.4)

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 of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with Zidovudine and 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 embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after the 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, the administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation losses 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 or 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 the following:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- Renal dysfunction, which may progress to renal failure with oligohydramnios

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 the limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Gastrointestinal disorders: 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 ibuprofen administration. Less frequently, gastritis has been observed. Gastrointestinal perforation has been reported with ibuprofen use. Pancreatitis has also been reported very rarely.

Immune system disorders:

Hypersensitivity reactions have been reported following treatment with NSAIDs.

These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiac disorders and vascular disorders:

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical studies suggest that use of ibuprofen, particularly at high dose (2400 mg/day), and in long term treatment, may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke (see section 4.4).

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Other adverse events reported less commonly and for which causality has not necessarily been established include:

Renal and urinary disorders: Impaired renal function and Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure

Hepatobiliary disorders: Abnormal liver function, hepatic failure, hepatitis and jaundice

Nervous system disorders: Visual disturbances, optic neuritis, headaches, paraesthesia, dizziness, somnolence

Eye disorders: Visual impairment and toxic optic neuropathy

Infections and infestations: Rhinitis and *reports* of aseptic meningitis (especially in patients with existing auto-immune disorders such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (See section 4.4).

Psychiatric disorders: *Insomnia*, *anxiety*, depression, confusion, hallucinations

Ear and labyrinth disorders: hearing impaired, tinnitus, vertigo

General disorders and administration site disorders: malaise, fatigue and drowsiness

Blood and lymphatic system disorders: Leukopenia, Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia

Skin and subcutaneous disorders: Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare), and photosensitivity reaction; fixed drug eruptions (unknown frequency), Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) (unknown frequency)

Paediatric population

No data available

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Signs and symptoms of toxicity have generally not been observed at doses below 100mg/kg in children or adults. However, supportive care may be needed in some cases.

Symptoms:
Most patients who have ingested clinically important amounts of NSAIDs (Ibuprofen) will develop manifest symptoms within 4 to 6 hours.

The most frequently reported symptoms of overdose include nausea, vomiting, lethargy, drowsiness, epigastric pain, abdominal pain or more rarely diarrhoea.

Central nervous system (CNS) effects include Tinnitus, headache, dizziness convulsion, and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects and gastro intestinal bleeding, apnoea, and depression of the CNS and respiratory system have also been rarely reported.

The following are also possible: fainting and cardiovascular toxicity, including hypotension, bradycardia and tachycardia have been reported. 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. 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. Large overdoses are generally well tolerated when no other drugs are being taken.

In serious poisoning metabolic acidosis may occur.

Therapeutic measures/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

M01AE, Anti-inflammatory and anti-rheumatic products, non-steroids, Propionic acid derivatives.

Ibuprofen is a phenylpropionic acid derivative which has analgesic, anti-inflammatory and antipyretic actions. The drug's therapeutic effects as an NSAID is thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Clinical evidence demonstrates that when 400mg 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 400mg 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

Maize Starch
Microcrytalline Cellulose
Croscarmellose Sodium
Povidone
Colloidal Silicon Dioxide
Alginic Acid
Sodium Lauryl Sulfate
Sodium Starch Glycolate
Magnesium Stearate
Hydroxypropylcellulose
Hydroxypropylmethylcellulose
Polyethylene Glycol 400
Erythrosine Aluminium Lake (E127)
Titanium Dioxide (E171)

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original container. Keep the container tightly closed.

Blister packs: Do not store above 25ºC. Store in the original package.

6.5 Nature and contents of container

PP or HDPE tablet containers of 50, 56, 84, 100, 250 or 500 tablets.

or

Plastic tablet containers of 50 tablets.

or

Blister packs comprised of Aluminium foil (20µm) and PVC (250µm) enclosed in an outer carton containing 84 tablets.

6.6 Special precautions for disposal

Non applicable.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/09/2000

10 DATE OF REVISION OF THE TEXT

15/03/2018