Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen 200 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Ibuprofen 200 mg

Excipients with known effect: Also contains 18.67 mg Potassium per capsule.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

Transparent, oval shaped soft gelatin capsule, printed 'BL200' in white ink, containing clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and children over 12 years:
Ibuprofen 200mg soft capsules are indicated as an anti-inflammatory, analgesic and antipyretic for short term management of mild to moderate pain, fever and inflammation associated with headache, dental pain, period pain, muscular strain, neuralgia, rheumatic pain and migraine and for the management of the symptoms of head colds and influenza.

4.2 Posology and method of administration

Posology

Adults, the elderly and children over 12 years:

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

If in children and adolescents 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.

Adults, the elderly and children over 12 years: 200 - 400mg taken with water up to three times a day as required. Leave at least four hours between doses with a maximum of 1200mg in any 24 hour period.

Not for use by children under 12 years of age.

Elderly: NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed (See Section 4.4).

Method of administration
For oral administration and short-term use only.

4.3 Contraindications

- Hypersensitivity to the active substance or to 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 (NSAIDs).

- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Patients with a history of, or existing gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs. (See Section 4.4)
- Patients with severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV). See also Section 4.4
- Last trimester of pregnancy

4.4 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 GI and cardiovascular risks below).
If symptoms persist for more than 3 days, patients should be advised to consult their doctor.

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). Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

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 section4.5)

SLE and mixed connective tissue disease:
Caution is required in Systemic lupus erythematosus as well as those with mixed connective tissue disease - increased risk of aseptic meningitis (see section 4.8).

Renal:
Caution is required in 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.
The dose should be as low as possible and renal function should be monitored.

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 trial and epidemiological data suggest that the use of ibuprofen, particularly at high doses(2400 mg/daily) and in long term treatment 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.
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.

Impaired female 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.
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 should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

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. 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 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 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. Acute generalised exanthematous pustulosis (AGEP). 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.
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 this medicine in case of varicella.

Blood effects:
As NSAIDs can interfere with platelet function, they should be used with caution in patients with idiopathic thrombocytopenic purpura (ITP), intracranial haemorrhage and bleeding diathesis.

Masking of symptoms of underlying infections:
Ibuprofen can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Ibuprofen is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In nonhospital settings, the patient should consult a doctor if symptoms persist or worsen.

Important information regarding the ingredients of this medicine
This medicine contains 18.75 mg of Potassium per capsule. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen (like other NSAIDs) should be avoided in combination with:

- **Aspirin (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 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 with:

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

- **Antihypertensives and diuretics:** NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal {unction (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 ibuprofen 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). It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

- **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.

- **Aminoglycosides:** reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

- **Lithium:** decreased elimination of lithium.

- **Methotrexate:** decreased elimination of methotrexate.

- **Ciclosporin:** Increased risk of nephrotoxicity with NSAIDs.

- **Mifepristone:** NSAIDs should not be used for 8-72 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

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

- **Zidovudine:** Increased risk of haematological toxicity when NSIADs 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.

- **Probenecid:** reduction in metabolism and elimination of NSAID and metabolites.

- **Oral hypoglycaemic agents:** inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

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 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

Increased formation of oedema in the mother could occur.
Consequently, ibuprofen is contraindicated during the third trimester of pregnancy.

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

Fertility:
There is limited 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.

4.7 Effects on ability to drive and use machines

None expected at recommended dose and duration of therapy.

4.8 Undesirable effects

The list of the following adverse events relates to those experienced with ibuprofen at OTC doses (maximum 1200mg per day) in short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse events may occur.

Adverse events which have been associated with Ibuprofen are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

The adverse events observed most often are gastrointestinal in nature. Adverse events are mostly dose-dependent, in particular the risk of occurrence of gastrointestinal bleeding is dependent on the dosage range and duration of treatment. 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).

Tabulated list of adverse reactions

The list of the following adverse events relates to those experienced with ibuprofen at OTC doses (maximum 1200 mg per day), for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse events may occur.

System Organ Class	***Frequency***	***Adverse events***
Blood and lymphatic system disorders	Very rare	Haematopoietic disorders[1]
Immune system disorders	Uncommon	Hypersensitivity reactions consisting of[1]: urticaria and pruritus[2].
	Very rare	Severe hypersensitivity reactions. Symptoms could be: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock)[2].
Nervous system disorders	Uncommon	Headache
	Very rare	Aseptic meningitis[3]
Cardiac disorders	Very rare	Cardiac failure and oedema[4]
Vascular Disorders	Very rare	Hypertension[4]
Respiratory, Thoracic and Mediastinal Disorders	Very rare	Respiratory tract reactivity comprising of asthma, aggravated asthma, bronchospasm or dyspnoea[2]
Gastrointestinal disorders	Uncommon	Abdominal pain, dyspepsia[5] and nausea.
	Rare	Diarrhoea, flatulence, constipation and vomiting
	Very rare	Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis[6], Mouth ulceration and gastritis
	Not Known	Exacerbation of ulcerative colitis and Crohn's disease[7] (See section 4.4) (see section 4.4)
Hepatobiliary disorders	Very rare	Liver disorders
Skin and subcutaneous tissue disorders	Uncommon	Various skin rashes[2]
	Very rare	Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis can occur[2].
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP), Photosensitivity reactions
Renal and urinary disorders	Very rare	Acute renal failure[8]
Infections and infestations	Very rare	Exacerbation of infections related inflammation (e.g. development of necrotizing fasciitis), in exceptional cases severe skin infections and soft-tissue complications may occur during a varicella infection.
Investigations	Very rare	Decreased haemoglobin levels, urea renal clearance decreased

[1] Examples include anaemia, leucopenia, thrombocytopenia, pancytopenia, and agranulocytosis. First signs are: fever, sore throat, superficial mouth ulcers and flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.
[2] Hypersensitivity reactions have been reported. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity, e.g. asthma, aggravated asthma, bronchospasm or dyspnea, or (c) various skin reactions, including

rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely, exfoliative and bullous dermatoses (including toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme).
[3] The pathogenic mechanism of drug-induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, single cases of symptoms of aseptic meningitis, (such as stiff neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease)
[4]Clinical studies suggest that the use of ibuprofen particularly at high doses (2400mg/day may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).
[5]The adverse events observed most often are gastrointestinal in nature.
[6]Sometimes fatal, particularly in the elderly
[7]See Section 4.4
[8]Especially in long-term use, associated with increased serum urea and oedema. Also includes papillary necrosis.

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 HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

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, 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 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propionic acid derivative ATC code: M01A E01

Mechanism of action
Ibuprofen is a propionic 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.

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 (acetylsalicylic acid) on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics studies show that when single doses of ibuprofen 400mg were taken within 8 h before or within 30 min after immediate release aspirin (acetylsalicylic acid) dosing (81mg), a decreased effect of ASA (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 relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Ibuprofen is well absorbed from the gastrointestinal tract. Ibuprofen is extensively bound to plasma proteins.

Ibuprofen 200mg liquid capsules consist of ibuprofen 200 mg dissolved in a hydrophilic solvent inside a gelatin shell. On ingestion, the gelatin shell disintegrates in the gastric juice releasing the solubilised ibuprofen immediately for absorption. The median peak plasma concentration is achieved approximately 30 minutes after administration.

The median peak plasma concentration for ibuprofen is achieved approximately 1-2 hours after administration.

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.

Elimination half-life is approximately 2 hours.

No significant differences in pharmacokinetic profile are observed in the elderly.

5.3 Preclinical safety data

The subchronic and chronic toxicity of ibuprofen in animal trials showed up mainly in the form of lesions and ulcers in the gastrointestinal tract.

In vitro and in vivo studies gave no clinically relevant evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found.

Ibuprofen led to an inhibition of ovulation in rabbits and impaired implantation in various animal species (rabbit, rat, mouse). Experimental studies in rat and rabbit have shown that ibuprofen crosses the placenta. Following administration of maternotoxic doses, an increased incidence of malformations (ventricular septal defects) occurred in the progeny of rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell
Gelatin
Polysorbate
Purified water

Capsule fill
Macrogol 600
Polysorbate 80
Potassium hydroxide
Purified water

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

Aluminium-PVC/PVDC blister packs containing 10, 12, 16, 18, 20, 24, 28, 30, 32, 36, 48, 96 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Brillpharma (Ireland) Limited
Inniscarra
Main Street
Rathcoole
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22749/022/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st May 2019
Date of last renewal: 5th December 2023

10 DATE OF REVISION OF THE TEXT

February 2024