BIORAJ PHARMACEUTICALS LIMITED	
BRAND NAME: BIORAJ IBUPROFEN CAPLETS	**GENERIC NAME: IBUPROFEN (400mg)**
SUMMARY OF PRODUCT CHARACTERISTICS	

1. NAME OF THE MEDICINAL PRODUCT

Bioraj Ibuprofen caplets B.P. 400 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each -coated caplet contains 400 mg Ibuprofen.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

An orange oval caplet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ibuprofen is indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and non-rheumatoid arthropathies. It is also indicated in other conditions such as frozen shoulder (capsulitis),bursitis, tendonitis, tenosynovitis, low back pain, soft tissue injuries (sprains and strains), dysmenorrhea, dental and post-operative pain and for symptomatic relief of headache, including migraine headache.

4.2 Posology and method of administration

Posology

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, dose can be increased until the acute phase is brought under control, provided that the total daily dose does not exceed 2400mg in divided doses.

Children: The daily dosage of Ibuprofen is 20mg/kg body weight in divided doses. In juvenile rheumatoid arthritis, Up to 40mg/kg body weight can be given daily in divided doses.

Not recommended for children weighing less than 7kg.

Elderly: The elderly are at increased risk of serious adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration and the patient should be monitored regularly for any sign of gastrointestinal bleeding. If renal or hepatic function is impaired, dosage should be assessed individually. Ibuprofen should be taken preferably with or after food.

Renal impairment

No dose adjustment is required in patients with mild to moderate impairment of renal function (for patients with severe renal insufficiency see section 4.3).

Hepatic impairment

No dose adjustment is required in patients with mild to moderate impairment of hepatic function (for patients with severe hepatic dysfunction see section 4.3).

Paediatric population

Contraindicated in children and adolescents below the age of 18 years (see section 4.3).

Method of administration

Oral use. The caplets should be swallowed whole with a glass of water.

4.3 Contraindications

Ibuprofen is contraindicated in patients who have previously shown hypersensitivity reactions (e.g asthma, urticaria, angioedema or rhinitis) after taking ibuprofen or other NSAIDs.
Ibuprofen is also contraindicated in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy, severe heart failure, hepatic failure, renal failure and in the last trimester of pregnancy.

Gastrointestinal (GI) effects

The use of with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors, Increases the risk of adverse reactions (see section 4.5) and should be avoided.
Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of GI events.
When GI bleeding or ulceration occurs in patients receiving ibuprofen, it is advised to withdraw the treatment.
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, 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 acetylsalicylic acid, or other medicinal products likely to increase GI risk (see below and section 4.5).
The patient is to be instructed to withdraw the medicinal product and to consult a physician immediately if severe pain in the upper abdomen or melaena or haematemesis occurs.
Patients with a history of GI toxicity, particularly the elderly, should be advised to report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

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

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 NSAIDSs (see section 4.8). Patients appear to be at highest risk of 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 and should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella may be associated with the onset of serious cutaneous and soft tissue infectious complications. Due to the potential of NSAIDs to worsen these infections, it is advisable to avoid use of ibuprofen in case of varicella.

Cardiovascular and cerebrovascular effects

Caution 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.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 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.

Hypersensitivity

Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are observed very rarely. At the first signs of hypersensitivity reaction (e.g. facial oedema, angioedema, dyspnoea, tachycardia, drop in blood pressure,anaphylactic shock) after taking/administering therapy must be stopped. The patient should be advised to immediately seek the assistance of a physician.

Effects on liver, renal and blood parameters

Ibuprofen may temporarily inhibit the blood-platelet function (thrombocyte aggregation). Therefore, patients with platelet disorders should be monitored carefully.

In case of prolonged treatment with ibuprofen, liver and kidney as well as blood parameters need to be checked regularly. First signs of haematopoietic disorders may be fever, sore throat, superficial wounds in the mouth, influenza-like complaints, severe lassitude, nosebleeds and skin bleeding.

Prolonged use of analgesics

Prolonged use of any type of analgesic for headaches can make them worse. If this situation is experienced or suspected, 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.

Concomitant alcohol consumption

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Caffeine

Excessive intake of caffeine (e.g. coffee, tea, foods, other drugs and beverages) should be avoided while taking this product (see section 4.9).

Particular caution is called for when using caffeine in patients with hyperthyroidism (risk of caffeine side effects) or arrhythmias.

4.4 Specific populations

Elderly patients are at higher risk of experiencing adverse reactions to NSAIDs especially GI bleeding and perforation, which may be fatal.

In the initial stages of treatment, careful monitoring of urine output and renal function is required in patients with heart failure, patients with chronically impaired renal or hepatic function, patients taking diuretics, patients who are hypovolaemic as a result of major surgery and, in particular, elderly patients.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of ibuprofen with: Possible effects:

Other NSAIDs, including salicylates: The concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. The concomitant use of ibuprofen with other NSAIDs should therefore be avoided.

Digoxin: The concomitant use of ibuprofen with digoxin preparations may increase serum levels of these medicinal products. A check of serum-digoxin is not required if used as recommended (maximum over 3 days).

Corticosteroids: Corticosteroids may increase the risk of adverse reactions, especially of the gastrointestinal tract (e.g. gastrointestinal ulceration or bleeding).

Anti-platelet agents: Increased risk of gastrointestinal bleeding.

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.

Anticoagulants: NSAIDs may enhance the effect of anti-coagulants .

Phenytoin: The concomitant use of ibuprofen with phenytoin preparations may increase serum levels of these medicinal products. A check of serum-phenytoin levels is not required if used as recommended (maximum over 3 days).

Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

Lithium: The concomitant use of ibuprofen with lithium preparations may increase serum levels of these medicinal products. A check of serum-lithium is not required if used as recommended (maximumover 5 days).

Probenecid and sulfinpyrazone: Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.

Diuretics, ACE inhibitors,

Betareceptor-blockers and angiotensinII antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive medicinal products. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, betareceptor-blockers or angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Potassium sparing diuretics: The concomitant administration of ibuprofen and potassium sparing diuretics may lead to hyperkalaemia. Check of serum potassium is recommended.

Methotrexate: The administration of ibuprofen within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryonic/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.

During the first and second trimester of pregnancy, ibuprofen is not recommended 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.

Breastfeeding

Ibuprofen and its metabolites can pass in low concentrations into the breast milk. No harmful effects to infants are known to date. Therefore, for short-term treatment with the recommended dose, 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.

4.7 Effects on ability to drive and use machines

As central nervous undesirable effects such as tiredness, dizziness and visual disturbances may occur with use of at high dosage, the ability to react and the ability to take part actively in road traffic and to operate machines may be impaired in isolated cases. This applies to a greater extent in combination with alcohol.

4.8 Undesirable effects

The list of the following undesirable effects comprises all undesirable effects that may occur under treatment with ibuprofen, also those under high-dose long-term therapy in rheumatism patients.

For ibuprofen containing drug products the most commonly observed adverse reactions are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly may occur. 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).

In one clinical trial investigating effect on pain after multimolar tooth extraction the frequency of Alveolar osteitis was reported to be 2.8% and aphthous stomatitis as 1.4%.

Patients should be informed that they should stop taking it immediately and consult a physician if they experience a serious adverse drug reaction.

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data).

4.9 Overdose

The symptoms of overdose can include CNS-related symptoms such as headache, dizziness, light-headedness and unconsciousness (also myoclonic convulsions in children), abdominal pain, nausea, vomiting, gastrointestinal bleeding and hepatic and renal dysfunction but also hypotension, respiratory depression and cyanosis. In serious poisoning metabolic acidosis may occur. A specific antidote does not exist.

Management of overdose

The 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, or gastric lavage. CNS symptoms and convulsions can be treated with benzodiazepines; supraventricular tachyarrhythmias can be controlled using ß-blockers such as propranolol, administered intravenously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids; Propionic acid derivatives

ATC code: M01AE51

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). Ibuprofen acts by blocking the production of prostaglandins (a chemical responsible for feeling pain, fever and inflammation) in the body.

Pharmacodynamics effects

In humans, ibuprofen reduces inflammatory-related pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation.

Experimental data suggests that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics studies show that when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Absorption

Following oral administration, ibuprofen is almost completely absorbed from the gastrointestinal tract. After oral doses 400-mg ibuprofen, peak plasma concentrations of 31.0 ± 17.2 µg/mL (Cmax) of ibuprofen were achieved within a median time of 1.5-1.9 hours (tmax). Concomitant administration with food may delay tmax about 2-fold. The geometric mean area under the concentration-time curve to the last measured point (AUC0-t ±%gCV) has been calculated as 133.0 ± 22.2 µg/mL/h.

Distribution

Plasma-protein binding amounts to about 99%. The apparent volume of distribution of ibuprofen after oral administration is about 0.1-0.2 L/kg. Ibuprofen can be transferred into human breast milk and its presence decreases with the protein concentration and the duration of lactation. The relative infant dose of ibuprofen has been quantified as ≤10%, which is considered to be safe even in preterm babies. Ibuprofen is expected to cross the blood-brain and the blood-cerebrospinal fluid barriers.

In synovial fluid, stable concentrations of ibuprofen of 5-8 mg/L are found between 2 and 8 h after administration. The synovial fluid Cmax is about one-third the Cmax in plasma.

Biotransformation

Biotransformation in the liver involves the conjugation of ibuprofen with glucuronic acid and oxidation yielding two main inactive metabolites, 2-hydroxyibuprofen and carboxyibuprofen. The degradation of ibuprofen is catalyzed by CYP2C9, CYP2C8 and CYP2C19.

Elimination

After 24 hours, 74.5% ± 9.6% of a 400-mg dose of ibuprofen is recovered in urine from which the amount of free active ibuprofen represents about 8%. The elimination half-life in

healthy individuals and those with liver and kidney diseases is 1.8 - 3.5 hours. The apparent clearance of ibuprofen after oral administration is about 0.05 – 0.1 L/h/kg.

6. Pharmaceutical Particulars

6.1 List of excipients

- Maize starch
- Methyl paraben
- Propyl paraben
- Gelatin
- Magnesium stearate
- Purified talc

Subcoating:

- Sucrose
- Gelatin
- Calcium carbonate
- Titanium dioxide
- Purified talc

Coloring and polishing

- Gelatin
- Sunset yellow
- Beewax
- Carnauba wax
- Chloroform

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30˚C. Protect from sunlight and moisture.

6.5 Nature and contents of container

10 caplets packed in alu –pvc blister, and each blister packed in a mono carton.

6.6 Special precautions for disposal

Not applicable

7.0 MANUFACTURER

Bioraj Pharmaceuticals Limited

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