SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:

Name of product

FLAMIFEN 400 (IBUPROFEN TABLETS BP 400 MG

Strength:

400 mg

Pharmaceutical form:

Sugar coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Name of Product	:	Flamifen 400 (Ibuprofen Tablets BP
400 mg) Batch Size	:	7,50,000 Tablets
Composition	:	Each Sugar Coated Tablet contains Ibuprofen BP ..... 400 mg
Description	:	Pink, circular, biconvex, sugar coated tablets plain on both sides
Product Expiry	:	36 Months
Packing	:	Blister pack of 10 X 10 tablets

Ingredient
Ibuprofen
Lactose
Polyvinyl Pyrrolidone
Maize Starch
Sodium Methyl Paraben
Sodium Propyl Paraben
Purified Water
Magnesium Stearate

Colloidal Anhydrous Silica
Talc
Sodium Starch Glycolate
Pharmagrade Sugar
Talc
Gelatin
Purified Water
Sodium Methyl Paraben
Sodium Propyl Paraben
Pharmagrade Sugar
Gelatin
Purified Water
Erythrosine
Titanium Dioxide
Sodium Methyl Paraben
Sodium Propyl Paraben
Carnauba Wax
Carbon Tetrachloride

3. PHARMACEUTICAL FORM:

Pink, circular, biconvex, sugar coated tablets plain on both the sides.

4. CLINICAL PARTICULARS:

i) Therapeutic indications:

Adults, elderly and Children over 12 years :

Rheumatic or muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

Children under 12 years of age: Not recommended

ii) Posology and method of administration:

For oral administration and short term use only.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms .

Adults, the elderly and children over 12 years :

The minimum effective dose should be used for the shortest time necessary to relieve the symptoms. The patient should consult a doctor if symptoms persist or worsen, or if Ibuprofen tablets are required for more than 10 days.

200mg – 400mg, to be taken up to three times a day as required.

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

If in adolescents (age range: ≥ 12 years to < 18 years) this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Children under 12 years of age:

Not recommended.

iii) Contraindications:

Hypersensitivity to Ibuprofen or any of the constituents in Ibuprofen tablets.

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

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

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

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

Severe hepatic failure, renal failure or severe heart failure (NYHA Class IV)

Last trimester of pregnancy .

iv) Special warnings and precautions for use:

Undesirable effects may be minimized by using the lowest effective dose for the shortest possible duration necessary to control symptoms .

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

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 .

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

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, and in the elderly. These patients should commence treatment on the lowest dose available.

Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal 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 .

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 ulcerative colitis or Crohn's disease as these conditions may be exacerbated .

Respiratory disorders

Caution is required if Ibuprofen is administered to patients suffering from, or with a previous history of, bronchial asthma or allergic disease since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular and cerebrovascular effects

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that

low dose ibuprofen (e.g. ≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required..

Renal:

Renal impairment as renal function may further deteriorate

There is a risk of renal impairment in dehydrated adolescents.

Hepatic:

Hepatic dysfunction .

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 .

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. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring within the first month of treatment in the majority of cases. Ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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. This is reversible upon withdrawal of treatment.

The label will include:

Read the enclosed leaflet before taking this product.

Do not take 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, consult your doctor.

v) Interaction with other FPPs and other forms of interaction

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 cardio protective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use .

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

Ibuprofen should be used with caution in combination with:

Anticoagulants: NSAIDS may enhance the effects of anti-coagulants, such as warfarin .

Antihypertensives, beta-blockers and diuretics: NSAIDs may reduce the effect of anti-hypertensives, such as ACE inhibitors, beta-blockers and diuretics.

Diuretics can also increase the risk of nephrotoxicity of NSAIDs. Corticosteroids: May increase the risk of adverse reactions in the gastrointestinal tract including gastrointestinal ulceration or bleeding .

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

Methotrexate: There is a potential for an increase in plasma methotrexate.

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.

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 coadministration 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.

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

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.

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

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.

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

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

vi) 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. 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.

At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the neonate to the following:

• Possible prolongation of bleeding time

• Inhibition of uterine contractions, which may result in delayed or prolonged labour.

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

Lactation

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

vii) Effects on ability to drive and use machines:

None expected at recommended doses and duration of therapy.

viii) Undesirable effects:

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:

Hypersensitivity reactions have been reported and these may consist of:

a) non-specific allergic reaction and anaphylaxis,

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

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

Uncommon: Hypersensitivity reactions with urticaria and pruritus.

Very rare: severe hypersensitivity reactions.

Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).

Exacerbation of asthma and bronchospasm.

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 .

Gastrointestinal disorders:

Uncommon: abdominal pain, nausea and dyspepsia.

Rare: diarrhoea, flatulence, constipation and vomiting.

Very rare: peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis. Exacerbation of colitis and Crohn's disease .

Unknown: pancreatitis

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 a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) .

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

Blood and lymphatic system disorders:

Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia Psychiatric disorders: Insomnia, anxiety, depression, confusional state, hallucination

Nervous System disorders:

Uncommon: Headache.

Renal and urinary disorders:

Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

Unknown: Impaired renal function and toxic nephropathy in various forms, including interstitial nephritis and nephrotic syndrome

Hepatobiliary disorders:

Very rare: liver disorders.

Haematological:

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

Skin and subcutaneous tissue disorders:

Uncommon: Various skin rashes

Very rare: Severe forms of skin reactions such as erythema multiforme and epidermal necrolysis can occur.

Unknown: Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, and photosensitivity reaction

Infections and infestations:

Unknown: Rhinitis and aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation .

Eye disorders:

Unknown: Visual impairment and toxic optic neuropathy

Ear and labyrinth disorders:

Unknown: Hearing impaired, tinnitus and vertigo

General disorders and administration site conditions:

Unknown: Malaise, fatigue.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

ix) 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 maintainance 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

i) Pharmacodynamic properties:

Pharmacotherapeutic group: NSAID

ATC code – M01AE01

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. 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.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid 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 cardio protective effect of low-dose Acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use .

ii) 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.

The half-life of Ibuprofen is approximately 2 hours.

In limited studies Ibuprofen appears in the breast milk in very low concentrations.

Ibuprofen is metabolised in the liver to two inactive metabolites and these, together with unchanged ibuprofen, are excreted by the kidney either as such or as conjugates. Excretion by the kidney is both rapid and complete.

Ibuprofen is extensively bound to plasma proteins.

6 PHARMACEUTICAL PARTICULARS:

i) List of Excipients:

Carbon Tetrachloride
Carnauba Wax
Colloidal Anhydrous Silica
Erythrosine
Gelatin
Lactose
Magnesium Stearate
Maize Starch
Pharmagrade Sugar
Polyvinyl Pyrrolidone
Purified Talc
Sodium Methyl Paraben
Sodium Propyl Paraben
Sodium Starch Glycolate
Titanium Dioxide

ii) Incompatibilities:

Not applicable.

iii) Shelf life:

36 Months

iv) Special precautions for storage:

Store in dry place at a temperature below 30°C .

v) Nature and contents of container:

Blister pack of 10 x 10 tablets.

vi) Special precautions for disposal:

Not applicable.

7. MARKETING AUTHORIZATION HOLDER:

OFFICE **:** 7/1, Corporate Park,
Sion-Trombay Road,
Chembur,
Mumbai 400 071.
INDIA
Phone Nos: 91-22- 30009205/04/202.
Fax: 91-22-25233085.
E.mail: ashf@giasbm01.vsnl.net.in
Website: www.flamingopharma.com

FACTORY **:** E-28, Opp. Fire Brigade Station,
M.I.D.C. Taloja. Dist. Raigad.
INDIA.
Tel: 91-22-39257758
Fax: 91-22-39257741

8. Number(s) in the National register of finised pharmaceutical products:

04600/06885/REN/2018

9. Date of first authorization/renewal of the Authorization :

05/10/2005

Last renewal: Aug 30, 2019

10. Date of revision of the text :

10/12/2015