SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gopain, 400 mg, Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg of Ibuprofen.

Excipient (s) with known effect:
Lactose anhydrous - 30 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gopain is indicated in adults for symptomatic treatment of the following conditions: slight intensity to moderate pain (rheumatic and muscular pain, back pain, neuralgia, migraine, headache, toothache, menstrual pain), fever and symptoms of colds and flu.

4.2 Posology and method of administration

Posology

The dosage varies according to the patient, his age and his medical condition.

The recommended dose is 1 tablet, up to 3 times per day (1200 mg) with a minimum interval of 6 to 8 hours.
Do not exceed the maximum daily dose of 3 tablets (1200 mg).
Do not use doses higher than recommended nor for more than 3 consecutive days for the fever, unless by express indication of the doctor.
Do not use in pain for more than 7 days unless otherwise prescribed by your doctor as prolonged and severe pain may require medical evaluation and treatment.

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

Administration Mode
Oral administration.
Tablets should be swallowed whole and with plenty of fluid, preferably after meals, to improve drug tolerability and reduce the likelihood of gastrointestinal problems.
Do not drink alcohol during treatment.

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- Hypersensitivity to other non-steroidal anti-inflammatory drugs (NSAIDs).
- Pregnancy and / or breastfeeding
- Patients with a history of asthma, rhinitis, urticaria, angioneurotic edema or bronchospasm associated with the use of acetylsalicylic acid or other NSAIDs.
-Depts with active ulcer or history of peptic ulcer or recurrent gastrointestinal bleeding (two or more distinct episodes of ulceration or proven bleeding), ulcerative colitis, Crohn's disease
-Daments with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy.
-Dentents with renal failure.
- Patients with hepatic impairment.
-Dentents with bleeding disorders (with a tendency to increase bleeding), cerebrovascular haemorrhage or other active bleeding.
- Significant dehydration (caused by vomiting, diarrhea or insufficient fluid intake);
- Severe heart failure (class IV of the NYPD Heart Association).
- Congenital disorder of porphyrin metabolism (eg acute intermittent porphyria).
- Chronic alcoholism (14-20 drinks / week or more)
- Patients with problems in the production of blood cells of unknown cause

4.4 Special warnings and precautions for use

In view of the status of the medicinal product (medicinal product not subject to a prescription exclusively dispensed in pharmacy), the medicinal product should not be dispensed with in the situations described below, except by medical indication:
- Ulcerative colitis, Crohn's disease
- Systemic Lupus Erythematosus (SLE) or other autoimmune diseases.
- Uncontrolled arterial hypertension, established cardiac ischemic disease, peripheral arterial disease, and / or cerebrovascular disease

The concomitant administration of Gopain with other NSAIDs, including selective cyclooxygenase-2 inhibitors, should be avoided.

Undesirable effects may be minimized by using the lowest effective dose for the shortest time needed to control symptoms (see section 4.2 and GI and cardiovascular risk information below).

Gopain should be used with caution in patients with a history of gastrointestinal disease.

Cases of potentially fatal bleeding, ulceration and gastrointestinal perforation have been reported with all NSAIDs at various stages of treatment, associated or not with warning symptoms or history of severe gastrointestinal events.
The risk of bleeding, ulceration or perforation is greater with higher doses of NSAIDs in patients with a history of peptic ulcer, especially if associated with bleeding or perforation (see section 4.3) and in elderly patients. In these situations patients should be instructed to inform their physician about the occurrence of abdominal symptoms and gastrointestinal bleeding, especially in the early stages of treatment.
In these patients treatment should be started at the lowest effective dose. Coadministration of protective agents (eg misoprostol or proton pump inhibitors) should be considered in these patients, as well as in those who need to take low dose acetylsalicylic acid at the same time or other medicinal products likely to increase the risk of ulcer or hemorrhage, such as corticosteroids, anticoagulants (such as warfarin), selective serotonin reuptake inhibitors, or antiplatelet agents such as acetylsalicylic acid (see section 4.5).
In case of gastrointestinal bleeding or ulceration in patients taking Holuren treatment should be discontinued.

NSAIDs should be administered with caution in patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease), insofar as these conditions may be exacerbated (see section 4.8).

Special precautions should be taken in patients with asthma or a previous history of bronchial asthma, as Ibuprofen may trigger bronchospasm in these patients.

Caution should be exercised in patients with renal, hepatic or cardiac insufficiency predisposed to hydrosaline retention, as the use of NSAIDs may impair renal function. In these patients the dose should be as low as possible and renal function should be monitored.

Like all NSAIDs, Ibuprofen can mask signs of infection.

At the start of treatment, Ibuprofen such as other NSAIDs should be administered with caution in patients with considerable dehydration.

Elderly patients have a higher frequency of adverse reactions with NSAIDs, especially gastrointestinal bleeding and perforation that can be fatal.

Ibuprofen should be used with caution in patients with systemic lupus erythematosus or other autoimmune diseases, for risk of aseptic meningitis and / or renal failure.

Hepatic function should be carefully monitored in patients treated with Ibuprofen who report symptoms compatible with liver damage (anorexia, nausea, vomiting, jaundice) and / or develop liver function abnormalities (transaminases, bilirubin, alkaline phosphatase, gamma-GT).
In the presence of transaminases, conjugated bilirubin or alkaline phosphatase values greater than 2 times the value of normal, the drug should be suspended immediately and investigation should be initiated to clarify the situation. Re-exposure to ibuprofen should be avoided.

Ibuprofen, like other NSAIDs, may inhibit platelet aggregation and prolong bleeding time in normal patients.

As with other NSAID-containing products, concomitant administration of Ibuprofen with acetylsalicylic acid is not recommended because of a potential increase in adverse effects.

Patients who report changes in vision during treatment with ibuprofen should discontinue therapy and be submitted to ophthalmologic examination.

Cardiovascular and cerebrovascular effects
Cases of fluid retention and edema have been reported in association with the administration of NSAIDs, so patients with a history of hypertension and / or mild to moderate congestive heart failure should be adequately monitored and advised.

Clinical studies suggest that the use of ibuprofen, particularly at a high dose (2400 mg / day), may be associated with a small increased risk of arterial thrombotic events (eg, myocardial infarction or stroke). In general, epidemiological studies do not suggest an association between the use of low-dose ibuprofen (eg, 1200 mg / day) and an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYII-III Heart Association), established ischemic heart disease, peripheral arteriopathy 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 given before initiating long-term treatment of patients with risk factors for cardiovascular events (eg, hypertension, hyperlipidemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg /day).

Serious skin reactions, some of which have been fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis associated with NSAID administration have been reported very rarely (see section 4.8). It appears that the risk of these reactions is greater at the beginning of treatment, and in most cases these reactions occur during the first month of treatment. Holuren should be discontinued at the first signs of rash, mucosal lesions, or other manifestations of hypersensitivity.

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

4.5 Interaction with other medicinal products and other forms of interaction

Lithium: NSAIDs may decrease renal clearance of lithium with a resulting increase in plasma levels and toxicity. If ibuprofen is prescribed for a patient on lithium therapy, close monitoring of lithium levels should be performed.

Methotrexate: Concomitant administration of an Ibuprofen and methotrexate may result in increased plasma methotrexate level, with the consequent increase of its toxicity.

Corticosteroids: increased risk of ulceration or gastrointestinal bleeding (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).

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

- Antiplatelet agents and selective serotonin reuptake inhibitors: increased risk of gastrointestinal bleeding (see section 4.4).

Diuretics, Angiotensin Converting Enzyme Inhibitors (ACEI), and Angiotensin II Antagonists (AAII): Non-steroidal anti-inflammatory drugs (NSAIDs) may decrease the effectiveness of diuretics as well as other antihypertensive drugs. In some patients with impaired renal function (eg, dehydrated or elderly patients with impaired renal function), coadministration of an ACEI or AAII and cyclooxygenase inhibitors may result in impaired renal function including the possibility of renal impairment acute, which is usually reversible. The occurrence of these interactions should be taken into consideration in patients taking ibuprofen in combination with ACE inhibitors or AAII. Therefore, this medicinal product should be administered with caution, especially in elderly patients. Patients should be adequately hydrated and the need to monitor renal function after initiation of concomitant therapy and periodically thereafter should be reviewed.

Ibuprofen also has interaction with:
- Cardiac glycosides (digoxin)

- Cholestyramine
- Cyclosporine
- Selective cyclooxygenase-2 inhibitors
- Ticlopidine
- Aminoglycosides; quinolones
- Ginkgo Biloba
- Mifepristone
- Tacrolimus
- Zidovudine
- CYP2C9 Inhibitors
- Oral antidiabetic agents (sulfonylureas)
- Phenytoin
- Probenecid or sulfimpyrazone

4.6 Fertility, pregnancy and lactation

Pregnancy:

Inhibition of prostaglandins synthesis may negatively affect pregnancy and/or the embryo-fetal development. Data from the epidemiological studies suggest an increased risk of spontaneous abortion, heart defects and of gastroschisis as a result of the use of an inhibitor of the prostaglandin synthesis in early pregnancy. The absolute risk of cardiovascular malformations increased with dose and duration of treatment.

In animals, it has been demonstrated that administration of prostaglandin synthesis inhibitors results in the increase of abortions peri and post-implantation and embryo-foetal mortality. Additionally, there was a higher incidence of multiple malformations, including cardiovascular malformations in animals exposed to prostaglandin synthesis inhibitors during the organogenetic period.

During the 1st and 2nd trimesters of pregnancy, Gopain should not be administered unless strictly necessary. If Gopain is used in women who are trying to become pregnant, or during the 1st and 2nd trimesters of pregnancy, the administered dose should be the lowest during the shortest period of time as possible.

During the 3rd trimester of pregnancy, all of prostaglandin synthesis inhibitors can expose the fetus to:
-Cardiopulmonary toxicity, with premature closing of *ductus arteriosus* (Botal channel) and pulmonary hypertension;
-Renal dysfunction, which may progress to renal failure with oligohydramnios.

In the final stage of pregnancy the mother and the newborn can be exposed to:
-possible prolongation of bleeding time, an antiplatelet effect that can occur even at very low doses;
-inhibition of uterine concentrations with a resulting delay or prolongation of the labor.

Thus, the administration of Gopain is contraindicated during the third trimester of pregnancy.

Lactation:
Due to the absence of clinical studies, the use of Gopain in women breast-feeding it is not recommended.

Fertility
Administration of Gopain may decrease female fertility and is therefore not recommended in women who plan to become pregnant. In women who have difficulty getting pregnant, or in whom the possibility of infertility is being investigated, Gopain discontinuation should be considered.

4.7 Effects on ability to drive and use machines

In single or short-term treatments, Gopain 400 mg Tablets does not interfere, in general, with the driving of vehicles or with the use of machines. However, due to the possibility of certain side effects, such as dizziness and confusion, the ability to drive and use machines may be compromised.

4.8 Undesirable effects

The side effects most frequently associated with the use of Ibuprofen are nausea, epigastric pain, dizziness and cutaneous erythema.

The adverse reactions described below are listed in order of decreasing frequency within each organ class.

Gastrointestinal disorders: The most frequently observed adverse events are gastrointestinal in nature. Potentially fatal peptic ulcers, perforation or gastrointestinal bleeding may occur, particularly in the elderly (see section 4.4). Nausea, dyspepsia, vomiting, haematuria, flatulence, abdominal pain, diarrhea, constipation, melena, aphthous stomatitis, exacerbation of colitis or Crohn's disease (see section 4.4) have been reported following the administration of these medicinal products. Less frequently cases of gastritis have been observed.

Hepatobiliary effects: Transient and slight transaminase elevations (ALT, AST), alkaline phosphatase and gamma-GT. Rare cases of severe, sometimes fatal, severe cytolytic or cholestatic hepatitis.

- Nervous system disorders: Vertigo, headache and nervousness. Depression, insomnia, confusion, emotional lability, drowsiness, aseptic meningitis with fever and coma. Paresthesias, hallucinations, and cerebral pseudotumor have been reported rarely.

- Cutaneous and subcutaneous tissue infections: Maculopapular cutaneous erythema and pruritus. Vesicle-bullous eruptions, urticaria, erythema multiforme, erythema nodosum,

Stevens-Johnson syndrome, alopecia and acne. Cases of toxic epidermal necrolysis (Lyell's syndrome) and photosensitivity reactions have been reported rarely.

-Ocular and ear operations: Tinnitus, decreased auditory acuity and amblyopia (blurred vision, scotomas and / or altered color vision). Rare cases of conjunctivitis, diplopia, optic neuritis and cataracts.

- Blood and lymphatic system disorders: Changes in coagulation, neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia, thrombocytopenia, eosinophilia and decreased hemoglobin.
Rare cases of epistaxis and menorrhagia.

- Endocrine disorders / metabolism: Decreased appetite. Rare cases of gynecomastia, hypoglycaemia and acidosis.

-Cardiopathies / Vascular disorders: fluid retention and palpitations. Rare cases of arrhythmia (sinus tachycardia or bradycardia). Edema, hypertension, and heart failure have been reported in combination with NSAIDs.
Clinical studies suggest that the use of ibuprofen, especially at a high dose (2400 mg / day), may be associated with a small increased risk of arterial thrombotic events (eg, myocardial infarction or stroke) (see section 4.4) .

Respiratory, thoracic and mediastinal disorders: Asthma, eosinophilic pneumopathy and bronchospasm.

Renal and urinary disorders: Renal (acute or chronic), decreased creatinine clearance, azotemia, polyuria, dysuria, and hematuria. Rare cases of renal papillary necrosis, acute tubulo-interstitial nephropathy and nephrotic syndrome.

-Other: Anaphylaxis, serum sickness, angioneurotic edema, Henoch-Schonlein vasculitis. Cases of ulcerous stomatitis, esophagitis, pancreatitis, rhinitis and fever have also been reported. Hyponatremia.

Notification of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the drug is important as it allows continuous monitoring of the drug's benefit-risk ratio. Health professionals are asked to report any suspected adverse reactions.

4.9 Overdose

The symptoms of acute intoxication with Ibuprofen are to a large extent those corresponding to exacerbation of undesirable effects.
In case of overdose, general common measures to other poisonings should be proceeded, such as gastric lavage and activated charcoal administration and special measures, such

as administration of antacids (and/or H2 antagonists), proper hydration and correction of the acidosis (if any) with sodium bicarbonate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivatives, Code ATC: M01A E01

Ibuprofen is a derivative of propionic acid with anti-inflammatory, analgesic and antipyretic action, presumably acting by inhibition of prostaglandin synthesis. Ibuprofen also appears to have an irreversible effect on platelet aggregation.
Some biochemical properties of ibuprofen, namely, inhibition of histamine synthesis and serotonin release, inhibition of bradykinin effects and inhibition of capillary permeability, could also contribute to its clinical effects.

Experimental data suggest that ibuprofen may, by competition, inhibit the effect of a low dose of acetylsalicylic acid on platelet aggregation when these drugs are administered concomitantly. Some pharmacodynamic studies have shown that when unit doses of ibuprofen 400 mg were taken up to 8 hours before or within 30 min after administration of immediate release acetylsalicylic acid (81 mg), there was a decrease in the effect of acetylsalicylic acid on the formation of thromboxane or in platelet aggregation. Although there are uncertainties about extrapolating these data to a clinical situation, it is not possible to rule out the possibility that regular and long-term use of ibuprofen may reduce the cardioprotection effect of a low dose of acetylsalicylic acid. Clinically relevant effects are not likely to occur with the occasional use of ibuprofen (see section 4.5).

5.2 Pharmacokinetic properties

Absorption and Distribution
Ibuprofen is rapidly absorbed from the gastrointestinal tract, reaching peak serum concentration 1-2 hours after administration. Ibuprofen binds strongly to plasma proteins.

Biotransformation and Elimination
Ibuprofen is metabolized in the liver in two inactive metabolites and these, along with unchanged Ibuprofen, are eliminated by the kidneys either in the unchanged or conjugated form. Elimination by the kidneys is rapid and complete.
The elimination half-life is approximately 2 hours.

5.3 Preclinical safety data

Ibuprofen toxicity in animal experiments was observed in the form of lesions and ulcerations of the gastrointestinal tract. In vitro and in vivo experiments have not revealed any mutagenic potential of Ibuprofen. Carcinogenicity studies in rats and mice have not

revealed any carcinogenic activity. Experimental studies have shown that Ibuprofen crosses the placenta, however, there isn't any evidence of teratogenic activity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Croscarmellose sodium
Lactose
Microcrystalline cellulose
Maize starch
Anhydrous colloidal silica (Aerosil 200)
Magnesium stearate
Titanium dioxide (E171)
Talc
Propylene glycol

6.2 Incompatibilities

The process of absorption of the active ingredient, Ibuprofen, is treated in the presence of alkalizing substances, namely antacids.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

PVC / PVDC / Alu blisters.
Packs of 20, 30 and 60 film-coated tablets.

It is possible that not all presentations may be marketed.

6.6 Special precautions for disposal

There are no special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Laboratórios Azevedos - Indústria Farmacêutica S.A.
Estrada Nacional 117-2, Alfragide
2614-503 Amadora
Portugal

8. MARKETING AUTHORIZATION NUMBERS

07275/08317/NMR/2020

9. DATE OF THE FIRST MARKETING AUTHORIZATION

Apr 13, 2022

10. DATE OF REVISION OF THE TEXT

07/2019