| | |
|---|---|
| **Brand Name : IBUGO-400 TABLETS**<br>**Generic Name :** IBUPROFEN BP 400 MG TABLETS | 2021 |
| | |
| **Module 1** Administrative Information and Product Information<br>**1.5** Product Information | **Confidential** |

**1.5 PRODUCT INFORMATION**

**1.5.1 Prescribing Information (Summary of Products Characteristics)**

# 1. NAME OF DRUG PRODUCT

## 1. Name of drug product

IBUPROFEN BP 400 MG TABLETS

## 1.1 (Trade) name of product

**IBUGO-400 TABLETS**

## 1.2 Strength

Each film tablet contains:
Ibuprofen BP 400 mg

## 1.3 Pharmaceutical Dosage Form

Film coated tablets

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS

## 2.1 Qualitative Declaration

Each film tablet contains:
Ibuprofen BP 400 mg

## 2.2 Quantitative Declaration

| Ingredients | Specification | Label Claim | Qty. / Tab. |
|---|---|---|---|
| **ACTIVE** | | | |
| Ibuprofen | BP | 400 mg | 400.00 mg |
| **NON ACTIVE** | | | |
| Micro Crystalline Cellulose powder | BP | - | 44.00 mg |
| Maize starch (10% extra added to compensate LOD.) | BP | - | 49.52 mg |
| Methyl Paraben Sodium | BP | - | 0.400 mg |
| Propyl Paraben Sodium | BP | - | 0.040 mg |
| Talcum | BP | - | 16.00 mg |
| Colloidal Silicon Dioxide | BP | - | 4.000 mg |
| Cross Carmellose Sodium | BP | - | 12.00 mg |
| Polacrillin Potassium ( Kyron T-314) | BP | - | 3.000 mg |
| Stearic acid | BP | - | 6.000 mg |
| Methylene Dichloride | BP | - | 151.071 mg |
| Iso propyl Alcohol | BP | - | 100.714 mg |
| Colour Instacoat Sol White 010 | BP | - | 13.250 mg |

BP = British Pharmacopoeia.

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# 3. PHARMACEUTICAL DOSAGE FORM

Film Coated tablets

White coloured, circular, biconvex film coated tablets.

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# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic Indications

Ibuprofen belongs to a group of medicines called NSAID (non-steroidal anti-inflammatory drugs) which work by reducing pain, inflammation and fever.

Ibuprofen is used for the symptomatic treatment of mild to moderate pain including migraine headache period pain and/or fever. In addition, Ibuprofen is used for the symptomatic treatment of pain and inflammation in arthritic diseases (e.g. rheumatoid arthritis), degenerative arthritic conditions (e.g. osteoarthritis) and in painful swelling and inflammation after soft tissues injuries.

## 4.2 Posology and Method of Administration

| **Age** | **Dose and how often to take** |
|---|---|
| **Adults, the elderly and children over 12 years** | Take 1 to 2 tablets up to 3 times a day, as required. Swallow tablets with a glass of water preferably with or after food. Do not take more often than every 4 hours. Do not exceed 6 tablets in 24 hours. |
| • This medicine is for short-term use only<br>• Take the lowest dose for the shortest time necessary<br><br>**In Adults:** Do not take Ibuprofen 200mg Tablets for longer than 10 days unless your doctor tells you to. Talk to a doctor or pharmacist if you do not get better or get worse, or if new symptoms occur.<br>**In Children and adolescents between 12 and 18 years:** If in children and adolescents this medicinal product is required for more than 3 days, or if symptoms worsen, a doctor should be consulted. | |
| **Do not give to children under 12 years.** | |

**Mild to moderate pain and fever**

Adults and adolescents older than 12 years (≥40 kg):
1-2 tablets given as a single dose or 3-4 times a day with an interval of 6 hours. The maximum daily dose should not exceed 6 tablets (1200 mg).

Children 6-12 years (>20 kg):
Children 6-9 years (20-29 kg): 1 tablet 1-3 times a day with intervals of 4 to 6 hours as required. The maximum number of tablets should not exceed 3 tablets in one day.

Children 10-12 years (30-40 kg): 1 tablet 1-4 times a day with intervals of 4 to 6 hours as required. The maximum number of tablets should not exceed 4 tablets in one day.

**Migraine headache**
Adults and adolescents older than 12 years (>40 kg):
2 tablets given as a single dose, if necessary
2 tablets with intervals of 4 to 6 hours.
The maximum daily dose should not exceed 6 tablets (1200 mg).

**Period pain**
Adults and adolescents over 12 years of age:
1-2 tablets 1-3 times a day, with an interval of 4-6 hours, as needed. The maximum daily dose should not be more than 6 tablets (1200 mg).

**Rheumatic diseases**
Adults:
The recommended dose is 2-3 tablets daily in divided doses. Lower doses may be prescribed by your doctor. Due to the nature and severity of your condition, the doctor may increase your medication to a maximum of 12 tablets (2400 mg) daily, taken in 3 or 4 divided doses.

Adolescents from 15 to 17 years of age:
The recommended dose is 20 mg/kg to a maximum of 40 mg/kg body weight daily (max 2400 mg daily) in 3 to 4 divided doses.

The tablet should be swallowed with a glass of water, preferably after a meal. Patients with sensitive stomach are recommended to take Ibuprofen during a meal. For the ease of swallowing or adjusting of doses the tablets can be divided in equal halves.

If a child or adolescent requires this medicine for more than 3 days, or if symptoms worsen, a doctor should be consulted

## 4.3 Contraindications

Ibuprofen tablets are contraindicated in patients with known hypersensitivity to Ibuprofen.
Ibuprofen tablets should not be given to patients who have experience asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.
Ibuprofen tablets are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

## 4.4 Special Warnings and Precautions for Use

Anti-inflammatory / pain-killer medicines like ibuprofen may be associated with a small increased risk of heart attack or stroke, particularly when used at high doses. Do not exceed the recommended dose or the duration of treatment.

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## 4.5 Interaction with Other Drugs, Other Forms of Interactions

❖ Ibuprofen may affect or be affected by some other medicines.
For example:

- other NSAIDs including COX-2 inhibitors, since this may increase the risk of gastrointestinal ulcers and bleeding
- anticoagulants (against clotting) such as warfarin or heparin, since the effect of the anticoagulant may be enhanced
- platelet aggregation inhibitors (against clotting) such as clopidogrel and ticlopidine
- methotrexate (used to treat cancer and auto-immune diseases)
- digoxin (for treatment of various heart conditions) since the effect of digoxin may be enhanced
- phenytoin (used in prevention of the occurrence of epileptic seizures) since the effect of phenytoin may be enhanced
- lithium (used to treat depression and mania) since the effect of lithium may be enhanced
- diuretics (water tablets) since the effect of the diuretics may be weakened,
- potassium-sparing diuretics since this may lead to hyperkalaemia
- medicines that reduce high blood pressure (ACE-inhibitors such as captopril, beta-blockers such as atenolol medicines, angiotensin-II receptor antagonists such as losartan)
- cholestyramine (used in the treatment of high cholesterol)
- aminoglycosides (medicines against certain types of bacteria) since NSAIDs may decrease excretion of aminoglycosides
- SSRIs (medicines against depression) such as paroxetin, sertralin, citalopram as these may increase risk of gastrointestinal bleeding
- ciclosporine, tacrolimus (for immuno-suppression after organ transplant) since kidney damage may occur.
- zidovudine or ritanovir (used to treat patients with HIV)
- mifepristone since NSAIDs can reduce the effect of mifepristone
- probenecid or sulfinpyrazone (for treating gout) since the excretion of ibuprofen may be delayed
- quinolone antibiotics since the risk of convulsions (fits) may be increased
- sulphonylureas (to treat type 2 diabetes) since the blood sugar levels can be affected
- glucocorticoids (used against inflammations) since this may increase the risk of gastrointestinal ulcers or bleeding
- bisphosphonates (used in osteoporosis, Paget's disease and to reduce high blood calcium levels)
- oxpentifylline ((pentoxifylline) used in the treatment of circulatory disease of the arteries of the legs or arms)
- baclofen (a muscle relaxant) because of elevated baclofen toxicity
- Gingko biloba herbal medicine (there is a chance you may bleed more easily if you are taking this with ibuprofen).

- voriconazole and fluconazole (CYP2C9 inhibitors) (used for fungal infections), since the effect of ibuprofen may increase. Reduction of the ibuprofen dose should be considered, particularly when high-dose ibuprofen is used with either voriconazole or fluconazole.

Some other medicines may also affect or be affected by the treatment of Ibuprofen. You should therefore always seek the advice of your doctor or pharmacist before you use Ibuprofen with other medicines.

## 4.6 Use in Pregnancy and Lactation

Do not take ibuprofen tablets if you are in the last 3 months of pregnancy. Talk to your doctor before taking ibuprofen tablets if you are in the first 6 months of pregnancy or are breastfeeding.
Ibuprofen 400mg Tablets belong to a group of medicines which may affect fertility in women. Fertility goes back to normal when you stop taking the medicine. It is unlikely that if you only take these tablets occasionally it will affect your chances of becoming pregnant. If you have problems becoming pregnant talk to your doctor before taking this medicine.

## 4.7 Effects on ability to drive and operate machine

Ibuprofen generally has no adverse effects on the ability to drive or operate machinery. However since at high dosage side effects such as fatigue, somnolence, vertigo (reported as common) and visual disturbances (reported as uncommon) may be experienced, the ability to take part actively in road traffic or operate machinery may be impaired in individual cases. This effect is potentiated by simultaneous consumption of alcohol.

## 4.8 Undesirable effects

Very common:
- heartburn, abdominal pain, indigestion

Uncommon:
- visual distrubances
- hypersensitivity reactions such as hives, itching, purpura, exanthema, asthma attacks (sometimes with low blood pressure)
- photosensitivity (increased sensitivity to sunlight)

Rare:
- vision loss

Very rare:
- sudden filling of lungs with water resulting in difficulty to breathe, high blood pressure, water retention and weight gain

Other possible side effects with Ibuprofen are:

Very common:
- Disturbances in the digestive tract, such as diarrhoea, feeling sick, vomiting, wind, constipation

Common:

- Digestive tract ulcer with or without perforation
- Bowel inflammation and worsening of inflammation of the colon (colitis) and digestive tract (Crohn's disease) and complications of diverticula of the large bowel (perforation or fistula)
- Microscopic bleeding from the intestine which may result in anemia
- Mouth ulcers and inflammation (ulcerative stomatitis)
- Headache, sleepiness, vertigo, dizziness, fatigue, agitation, insomnia and irritability

Uncommon:

- Inflammation of the stomach lining
- Kidney problems including development of oedema, inflammation of the kidneys and kidney failure
- Runny nose
- Difficulty breathing (bronchospasm)

Rare:

- Depression, confusion, hallucinations
- Lupus erythematosus syndrome
- Increase of blood urea nitrogen, serum transaminases and alkaline phosphatase decrease in haemoglobin and haematocrit values, inhibition of platelet aggregation and prolonged bleeding time, decrease of serum calcium and increase in serum uric acid values
- Damage of the kidney tissue

Very rare:

- Unpleasant awareness of heart beat, heart failure or heart attack
- Disorders of blood cell formation (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis, neutropenia) The first symptoms or signs may include fever, sore throat, surface mouth ulcers, flu- like symptoms, severe fatigue, nasal and skin bleeding)
- Ringing or buzzing in the ears
- Inflammation of the oesophagus or pancreas
- Narrowing of the bowel
- Acute inflammation of the liver, yellowish discolouration of the skin or whites of the eyes, liver dysfunction, damage or failure
- liver damage especially in long-term use or liver failure
- Hair loss

## 4.9 Overdoses

The symptoms of overdose are presented in individuals that consumed more than 99 mg/kg. Most common symptoms of overdose are abdominal pain, nausea, vomiting, lethargy, vertigo, drowsiness (somnolence), dizziness and insomnia. Other symptoms of overdose include headache, loss of consciousness, tinnitus, CNS depression, convulsions and seizures. May rarely cause metabolic acidosis, abnormal hepatic function, hyperkalemia, renal failure, dyspnea, respiratory depression, coma, acute renal failure, and apnea (primarily in very young pediatric patients).

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# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmaco-Kinetic Properties

**Absorption**

It is very well absorbed orally and the peak serum concentration can be attained in 1 to 2 hours after extravascular administration. When ibuprofen is administered immediately after a meal there is a slight reduction in the absorption rate but there is no change in the extent of the absorption.

When orally administered, the absorption of ibuprofen in adults is very rapidly done in the upper GI tract. The average Cmax, Tmax and AUC ranges around 20 mcg/ml, 2 h and 70 mcg.h/ml. These parameters can vary depending on the enantiomer form, route, and dose of administration.

**Volume of distribution**

The apparent volume of distribution of ibuprofen is of 0.1 L/kg.

**Protein binding**

Ibuprofen dosage is more than 99% bound to plasma proteins and site II of purified albumin, binding appears to be saturable and becomes non-linear at concentrations exceeding 20 mcg/ml.

**Metabolism**

Ibuprofen is rapidly metabolized and biotransformed in the liver to the formation of major metabolites which are the hydroxylated and carboxylated derivatives. As soon as it is absorbed, the R-enantiomer undergoes extensive enantiomeric conversion (53-65%) to the more active S-enantiomer *in vivo* by the activity of alpha-methylacyl-CoA racemase.

Ibuprofen metabolism can be divided in phase I which is represented by the hydroxylation of the isobutyl chains for the formation of 2 or 3-hydroxy derivatives followed by oxidation to 2-carboxy-ibuprofen and p-carboxy-2-propionate. These oxidative reactions are performed by the activity of the cytochrome P450 isoforms CYP 2C9, CYP 2C19 and CYP 2C8. Therefore, these enzymes participate in the oxidation of the alkyl side chain to hydroxyl and carboxyl derivatives. From this enzymes, the major catalyst in the formation of oxidative metabolites is the isoform CYP 2C9.

The metabolic phase I is followed by a phase II in which the oxidative metabolites may be conjugated to glucuronide prior to excretion. This activity forms phenolic and acyl glucuronides.

- Ibuprofen
  - Ibuprofen glucuronide
  - 2-Hydroxyibuprofen
  - 3-Hydroxyibuprofen
    - Carboxy-ibuprofen
  - 1-hydroxyibuprofen

**Route of elimination**

Ibuprofen is rapidly metabolized and eliminated in the urine thus, this via accounts for more than 90% of the administered dose. It is completely eliminated in 24 hours after the last dose and almost all the administered dose goes through metabolism, representing about 99% of the eliminated dose. The biliary excretion of unchanged drug and active phase II metabolites represents 1% of the administered dose.

In summary, ibuprofen is excreted as metabolites or their conjugates. The elimination of ibuprofen is not impaired by old age or the presence of renal impairment.

## 5.2 Pharmaco-dynamic properties

Ibuprofen has multiple actions in different inflammatory pathways involved in acute and chronic inflammation. The main effects reported in ibuprofen are related to the control of pain, fever and acute inflammation by the inhibition of the synthesis of prostanoids by COX-1 and COX-2. Pain relief is attributed to peripheral affected regions and central nervous system effects in the pain transmission mediated by the dorsal horn and higher spinothalamic tract. Some reports have tried to link the pain regulation with a possible enhancement on the synthesis of endogenous cannabinoids and action on the NMDA receptors. The effect on pain has been shown to be related to the cortically evoked potentials.

The antipyretic effect is reported to be linked to the effect on the prostanoid synthesis due to the fact that the prostanoids are the main signaling mediator of pyresis in the hypothalamic-preoptic region.

The use of ibuprofen in dental procedures is attributed to the local inhibition of prostanoid production as well as to anti-oedemic activity and an increase of plasma beta-endorphins. Some reports have suggested a rapid local reduction of the expression of COX-2 in dental pulp derived by the administration of ibuprofen.

The administration of ibuprofen in patients with rheumatic diseases has shown to control joint symptoms.

Ibuprofen is largely used in OTC products such as an agent for the management of dysmenorrhea which has been proven to reduce the amount of menstrual prostanoids and to produce a reduction in the uterine hypercontractility. As well, it has been reported to reduce significantly the fever and the pain caused by migraines. This effect is thought to be related to the effect on platelet activation and thromboxane A2 production which produces local vascular effects in the affected regions. This effect is viable as ibuprofen can enter in the central nervous system.

In the investigational uses of ibuprofen, it has been reported to reduce neurodegeneration when given in low doses over a long time. On the other hand, its

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use in Parkinson disease is related to the importance of inflammation and oxidative stress in the pathology of this condition. The use of ibuprofen for breast cancer is related to a study that shows a decrease of 50% in the rate of breast cancer.

## 5.3 Pre-clinical safety data

Ibuprofen sub chronic and chronic toxicity was mainly shown by animal testes as gastric tract damage and ulcer.

The vitro and in vitro tests have not shown any clinically significant signs about ibuprofen mutagenicity. Furthermore no carcinogenic effects have been observed in mice and rats.

Ibuprofen inhibits ovulation in rabbits and impairs implantation in various animal species. In reproduction tests undertaken with rats and rabbits, ibuprofen passed across the placenta. When using doses toxic to mother, malformations occue more frequently.( i.e. ventricular septum defects).

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# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of Excipients

| | | | |
|---|---|---|---|
| 1. Micro Crystalline Cellulose powder | BP | 44.00 | mg |
| 2. Maize starch (10% extra added to compensate LOD.) | BP | 49.52 | mg |
| 3. Methyl Paraben Sodium | BP | 0.400 | mg |
| 4. Propyl Paraben Sodium | BP | 0.040 | mg |
| 5. Talcum | BP | 16.00 | mg |
| 6. Colloidal Silicon Dioxide | BP | 4.000 | mg |
| 7. Cross Carmellose Sodium | BP | 12.00 | mg |
| 8. Polacrillin Potassium ( Kyron T-314) | BP | 3.000 | mg |
| 9. Stearic acid | BP | 6.000 | mg |
| 10. Methylene Dichloride | BP | 151.071 | mg |
| 11. Iso propyl Alcohol | BP | 100.714 | mg |
| 12. Colour Instacoat Sol White 010 | BP | 13.250 | mg |

## 6.2 Incompatibilities

None reported

## 6.3 Shelf-Life

36 months from the date of manufacture.

## 6.4 Special Precautions for Storage

Store below 30°C.
Protect from light.