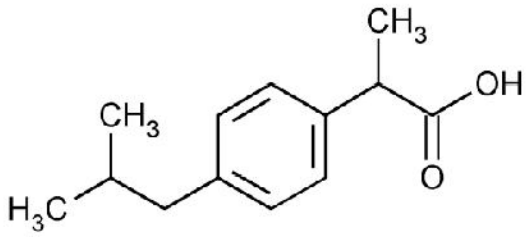
APO-IBUPROFEN 400

NAME OF THE MEDICINE

Ibuprofen
The structural formula for ibuprofen is shown below:



Chemical formula: $C_{13}H_{18}O_2$
Molecular weight: 206.3
CAS Number: 15687-27-1

DESCRIPTION

Active ingredient: Ibuprofen 400 mg

Ibuprofen is a (±)-2-(*p*-isobutylphenyl) propionic acid. Ibuprofen is a white crystalline solid with a melting point of 74 – 77°C and is practically insoluble in water (< 0.1mg/mL) and readily soluble in organic solvents such as ethanol and acetone.

Excipients: Lactose monohydrate, cellulose microcrystalline, povidone, croscarmellose sodium, sodium lauryl sulfate, colloidal silica anhydrous, stearic acid, macrogol 6000, hypromellose, titanium dioxide and talc purified.

PHARMACOLOGY

Pharmacokinetics

Absorption: Ibuprofen is well absorbed from the gastrointestinal tract. It is highly bound (90-99%) to plasma proteins and is extensively metabolized to inactive compounds in the liver, mainly by glucuronidation. Both inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion. The elimination half-life of ibuprofen is in the range of 1.9 to 2.2 hours.

Pharmacodynamics/Mechanisms of action

Ibuprofen possesses analgesic, antipyretic anti-inflammatory properties, similar to other non-steroid anti-inflammatory drugs (NSAIDs). Its mechanism of action is unknown, but is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthetase inhibition.
Ibuprofen has shown anti-inflammatory, analgesic and antipyretic activity in both animal and human studies. These properties provide symptomatic relief of inflammation and pain in rheumatoid arthritis, osteoarthritis and allied conditions.

CINICAL TRIALS

This information is not available.

INDICATIONS

For the temporary relief of pain and/or inflammation associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches and pains, period pain, sore throat, tennis elbow, arthritis, rheumatic pain and aches and pains associated with colds and flu. Reduces fever.

CONTRAINDICATIONS

Ibuprofen is contraindicated for use in patients with:

- known hypersensitivity or idiosyncratic reaction to ibuprofen (or any of the inactive ingredients)
- known hypersitivity to aspirin and other NSAIDs
- asthma that is aspirin or NSAID sensitive
- active gastrointestinal bleeding or peptic ulceration
- renal impairment
- heart failure
- severe liver impairment
- undergoing treatment of perioperative pain in a setting of coronary artery bypass surgery (CABG)

Use of ibuprofen is contraindicated during the third trimester of pregnancy.
Ibuprofen should not be taken with other products containing ibuprofen or with other anti-inflammatory medicines.

PRECAUTIONS

Ibuprofen should be used with caution in patients with:

- Previous history of gastrointestinal haemorrhage or ulcers
- Asthma who have not previously taken NSAID
- Hepatic, or cardiac impairment
- Pregnancy (See 'Use in Pregnancy')
- Elderly (See 'Use in Elderly')
- Ibuprofen should be taken with caution with other products containing aspirin or salicylates.

As with other NSAIDs, excessive use of ibuprofen may increase the risk of heart attack, stroke or liver damage in both patients with predisposing cardiovascular risk factors and in normal patients.

Refer to 'INTERACTIONS WITH OTHER MEDICINES' for additional information

Cardiovascular and cerebrovascular effects

Observational studies have indicated that NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use.
Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk.
Patients should be advised to remain alert for such cardiovascular events, even in the absence of previous cardiovascular symptoms. Patients should be informed about signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.
Fluid retention, hypertension and oedema have been reported in association with NSAID therapy. Patients taking antihypertensives with NSAIDs may have an impaired antihypertensive response.
APO-Ibuprofen 400 tablets should be used with caution in patients with hypertension (see also Contraindications – heart failure).

Gastrointestinal (GI)

NSAIDS should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (See Adverse effects).
Gastrointestinal GI bleeding, ulceration and 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 serious GI events. The frequency of such events may increase with dose or duration of use. Patients at most risk of developing

these types of GI complications with NSAIDs are the elderly, patients using concomitant aspirin, patients with a history of, or active GI disease (eg.ulceration, GI bleeding or inflammatory conditions) and patients with a history of smoking and alcoholism.
Ibuprofen should be used only under medical advice in:
− Patients with previous history of GI haemorrhage or ulcers (see also Contraindications – active GI bleeding or peptic ulceration). Patients should report any new or unusual abdominal symptoms during treatment. If GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn immediately. Appropriate clinical evaluation and treatment should be considered.
− 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 or other NSAIDs including cyclooxygenase-2 (COX-2) selective inhibitors.

Hepatic

As with other NSAIDs elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in controlled clinical trials in less than 1% of patients.

Patients should be advised to remain alert for hepatotoxicity and be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritus, jaundice, abdominal tenderness in the right upper quadrant and “flu-like” symptoms).

Respiratory

Ibuprofen should be used only under medical advice in patients with, or a previous history of, bronchial asthma or allergic disease because bronchospasm may be precipitated in these patients.

SLE and mixed connective tissue disease

Ibuprofen should be used with caution in patients with systemic lupus erythematosus and mixed connective tissue disease as there is a risk of increased aseptic meningitis

Dermatological

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 Adverse Effects). These serious adverse events are idiosyncratic and are independent of dose or duration of use. 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. Ibuprofen use should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity and medical advice should be sought immediately.
This product should not be taken with other medicines containing ibuprofen, aspirin or other anti-inflammatory medicines or other medicines being taken regularly unless under medical advice.’.

Effects on fertility

The use of ibuprofen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

USE IN PREGNANCY (CATEGORY C)

Ibuprofen inhibits prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation and may delay labour and birth. Use of ibuprofen is thus contraindicated during the third trimester of pregnancy, including the last few days before expected birth.

Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy.

Further, there is insufficient experience about the safety of use of ibuprofen in humans during pregnancy. APO-Ibuprofen 400 tablets should therefore not be used during the first 6 months of pregnancy unless the potential benefits to the patient outweigh the possible risk to the foetus.

Use in Lactation

Ibuprofen appears in breast milk in very low concentrations and is unlikely to affect the breast fed infant adversely.

Use in the elderly

Ibuprofen should not be taken by adults over the age of 65 without careful consideration of co-morbidities and co-medications because of an increased risk of adverse effects, in particular heart failure, gastro-intestinal ulceration and renal impairment (see also Contraindications – renal impairment, heart failure).

INTERACTIONS WITH OTHER MEDICINES

The following interactions with ibuprofen have been noted:

- *Anticoagulant-including warfarin*: Ibuprofen interferes with the stability of INR and may increase the risk of severe bleeding and sometimes-fatal haemorrhage, especially from the gastrointestinal tract. Ibuprofen should only be used in patients taking warfarin if absolutely necessary and they must be closely monitored
- *Lithium*: Ibuprofen may decrease the renal clearance and increase plasma concentrations of lithium.
- *Cardiac glycosides*: NSAIDs may increase plasma glycoside levels.
- *Ciclosporin:* Increased risk of nephrotoxicity.
- *Corticosteroids*: An increased risk of gastrointestinal bleeding may occur with corticosteroids.
- *Methotrexate*: Ibuprofen reduces methotrexate clearance.
- *Mifepristone:* NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
- *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.
- *Tacrolimus:* possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- *Zidovudine*: Concurrent administration with ibuprofen may prolong bleeding time in patients.
- *Antidiabetic medicines, Probenecid and phenytoin*: Interactions may also occur with probenecid and phenytoin.
- *ACE inhibitors, beta-blockers and diuretics*: Ibuprofen, like other NSAIDs may reduce the antihypertensive effect of ACE inhibitor and beta-blockers and diuretics and may cause natriuresis and hyperkalemia in patients under these treatments. Combination use of an ACE inhibitor or angiotensin receptor antagonist, and anti-inflammatory drug (NSAID or COX-2 inhibitor) and a diuretic increases the risk of renal impairment. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.
- *NSAIDs and aspirin*: Concurrent use of ibuprofen with aspirin or other NSAIDs can lead to increased gastrointestinal adverse effects.

Lactose

This medicine contains lactose monohydrate. Patients with rare hereditary forms of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption syndrome should not take this medicine.

ADVERSE EFFECTS

Adverse effects with non-prescription (OTC) or short-term use ibuprofen are rare and may include:

- Gastrointestinal-dyspepsia, heartburn, nausea, loss of appetite, stomach pain, diarrhea
- Central nervous system (CNS) –dizziness, fatigue, headache, nervousness
- Hypersensitivity reactions – skin rashes and itching. Rarely exfoliative dermatitis and epidermal necrolysis have been reported with ibuprofen

- Rare cases of photosensitivity
- Cardiovascular fluid retention and in some cases oedema. These effects are rare at non-prescription doses.

Allergic reactions such as skin rash, itching, swelling of the face or breathing difficulties may also occur. These are usually transient and reversible on cessation of treatment.

The frequencies of adverse effects are defined as follows:
Very common: *>1/10*
Common: *>1/100, <1/10*
Uncommon: *>1/1,000, <1/100*
Rare: *>1/10,000, <1/1,000*
Very Rare: *<1/10,000,* including isolated reports.

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of
a) non-specific allergic reactions and anaphylaxis
b) respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm, dyspnea.
c) Assorted skin disorders, including rashes of various types, pruritius, urticaria, urpura, angioedema and more rarely bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The following 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.

Blood and Lymphatic System Disorders:

Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia and agranulocytosis).

Hypersensitivity reactions:

Uncommon: Hypersensitivity reactions with urticaria and pruritius
Very rare: severe hypersensitivity reactions. Symptoms could be facial, tongue and larynx, swelling, dyspnoea, apnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock - syndrome may be characterised by abdominal pain, fever, shivering, nausea and vomiting. Exacerbation of asthma and bronchospasm.
Hepatotoxicity and aseptic meningitis which occur less frequently may also be hypersensitivity reactions.

Allergic reactions such as skin rash, itching, swelling of the face or breathing difficulties are usually transient and reversible on cessation of treatment.

Gastrointestinal disorders:

The most commonly observed adverse events are gastrointestinal in nature.
Uncommon: abdominal pain, nausea, dyspepsia
Rare: Diarrhoea, flatulence, heartburn, loss of appetite, constipation and vomiting
Very rare: peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis.
Exacerbation of ulcerative colitis and Crohn's, disease, Gastric pyrosis.

Nervous System:

Uncommon: Headache
Very rare: Aseptic meningitis - single cases have been reported, Dizziness, nervousness, tinnitus, depression, drowsiness, insomnia, irritability, difficulty in concentrating, emotional instability, convulsions, auditory and visual problems.
Rare: fatigue

Renal:

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

Ibuprofen may cause cystitis and haematuria, interstitial nephritis, nephrotic syndrome, oliguria, tubular necrosis, glomerulonephritis, alteration in the renal function test, polyuria.

Liver:

Very rare: liver disorders, especially in long term treatment, including hepatotoxicity, hepatitis, jaundice, alterations of hepatic function tests, pancreatitis, duodenitis, oesophagitis, hepato-renal syndrome, hepatic necrosis, hepatic insufficiency.

Haematological:

Very rare: Haematopoietic disorders (anaemia, neutropenia, aplastic anaemia, haemolytic anaemia, eosinophilia, reduction of haemoglobin and haematocrit leucopenia,thrombocytopenia, pancytopenia, agranulocytosis). Reversible platelet aggregation, alveolitis, pulmonary eosinophilia, pancreatitis.

Dermatological:

Uncommon: Various skin rashes
Very rare: Severe forms of skin reactions such as bullous reactions including Stevens Johnson Syndrome, erythema multiform and toxic epidermal necrolysis can occur.
Rarely skin peeling, alopecia, exfoliative dermatitis, photosensitive dermatitis, maculopapular, Rash.

Immune System:

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.

Cardiovascular and Cerebrovascular:

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.
Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).
Rarely: cerebrovascular accidents, hypotension, congestive cardiac insufficiency in patients with compromised cardiac function, palpitations.

Ocular:

Very rare: Blurred vision, changes in visual colour perception, toxic amblyopia, episodes of ocular alteration with consequent visual disorders.

Other:

Effect on the endocrine system and on the metabolism, reduction in appetite.
Rarely: dryness of the eyes and mouth, gingival ulcers, rhinitis, hearing disturbances.

DOSAGE AND ADMINISTRATION

Adults and children 12 years and over

The recommended dose is one tablet to be taken every 4 to 6 hours as necessary. (Maximum 3 tablets in 24 hours).

Do not exceed the recommended dose.

Children under 12 years

APO-Ibuprofen 400 should not be administered to children aged less than 12 years.

This product should not be used for more than 3 days at a time except on medical advice, in which case the patient should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.

OVERDOSAGE

In case of overdose, immediately contact the Poisons Information centre (in Australia please call 13 11 26 and in New Zealand 0800 764 766) for advice.

Symptoms include nausea, abdominal pain and vomiting, dizziness, convulsion and rarely, loss of consciousness. Clinical features of overdose with ibuprofen which may result are depression of the central nervous system and the respiratory system.
There is no specific antidote to ibuprofen.

PRESENTATION AND STORAGE CONDITIONS

White to off-white, pillow-shaped, film coated tablets, plain on both sides.

APO-Ibuprofen 400 tablets (Aust R 289218) do not contain gluten, wheat, sucrose or preservatives.
Available in cartons with PVC/Aluminium blister packs containing 10, 20, or 30 * tablets
* Not all pack sizes may be marketed.

Storage:

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
AUSTRALIA

POISON SCHEDULE OF THE MEDICINE

S3 – Pharmacist Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG): 22 May 2017