

## DATA SHEET

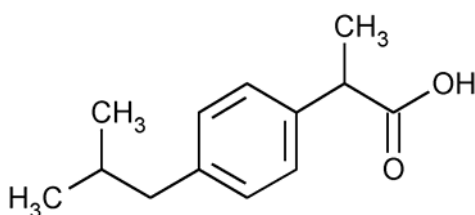
### BRUFEN®

200mg, 400mg and 600mg tablet

#### NAME OF MEDICINE

Ibuprofen 200mg, 400mg and 600mg

The structural formula for ibuprofen is shown below:



CAS Number: 15687-27-1

#### DESCRIPTION

Ibuprofen is a (±)-2-(p-isobutylphenyl) propionic acid. Ibuprofen is a white crystalline solid with a melting point of 74 - 77°C and is very slightly soluble in water (< 1mg/mL) and readily soluble in organic solvents such as ethanol and acetone.

#### PHARMACOLOGY

Ibuprofen is a nonsteroidal anti-inflammatory agent that possesses analgesic and antipyretic activities. Its mode of action, like that of other nonsteroidal anti-inflammatory agents, is not completely understood, but may be related to 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.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

## ***Pharmacokinetics***

### Absorption

Ibuprofen is well absorbed after oral administration. Single doses of 200 mg taken on an empty stomach by volunteers produced peak serum levels after approximately 45 minutes. When taken after food, absorption was slower, peak levels appearing at 1.5 to 3 hours.

### Bioavailability

The bioavailability of ibuprofen from one Brufen 400 mg tablet is equivalent to that from two Brufen 200 mg tablets, and 20mL of a 2% Brufen Syrup.

### Distribution

Apparent volume of distribution is 0.14 L/kg. Ibuprofen and its metabolites readily cross the placental barrier in pregnant rabbits and rats. It is not known if ibuprofen enters the CSF or is excreted in milk.

### Protein binding

99% of ibuprofen is protein bound. The high protein binding of ibuprofen should be borne in mind when prescribing ibuprofen together with other protein bound drugs which bind to the same site on human serum albumin.

### Metabolism

About 90% of ibuprofen is metabolised to two major metabolites (A and B); these are as follows:

Metabolite A (+) 2-4-(2-hydroxy-2-methylpropylphenyl) propionic acid

Metabolite B (+) 2-4-(2-carboxypropylphenyl) propionic acid.

Both metabolites are dextrorotatory and are devoid of anti-inflammatory and analgesic activity.

Normal volunteers and patients with rheumatoid arthritis were given ibuprofen 800 mg as a single dose. After 14 to 24 hours the plasma levels of ibuprofen and metabolites were less than 0.25 microgram/mL.

### Excretion

The kidney is the major route of excretion. 95% of ibuprofen was excreted in the urine within 24 hours of a single dose of 500 mg; 35% as metabolite A (15 % free, 20% conjugated), 51% as metabolite B (42% free, 9% conjugated), ibuprofen 9% (1% free, 8% conjugated).

### Half-life

Plasma half-life of ibuprofen is in the range 1.9 to 2.2 hours.

## INDICATIONS

Rheumatoid arthritis  
Osteoarthritis  
Juvenile rheumatoid arthritis  
Primary dysmenorrhoea  
Pyrexia

Brufen is also indicated for the relief of acute and/or chronic pain states in which there is an inflammatory component.

## CONTRAINDICATIONS

Known hypersensitivity to ibuprofen or any of the inactive ingredients. Hypersensitivity (e.g. asthma, rhinitis or urticaria) to aspirin or other nonsteroidal anti-inflammatory drugs. Ibuprofen should not be used in active gastrointestinal bleeding or perforation, related to previous NSAID therapy. Ibuprofen should not be used in patients with active, or a history of, ulcerative colitis, Crohn's disease, recurrent peptic ulceration or gastrointestinal hemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding).

Pregnancy - see Use in Pregnancy

Lactation - see Use in Lactation

## PRECAUTIONS

### **Cardiovascular Thrombotic Events**

Observational studies have indicated that non-selective 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 or cardiovascular risk factors may also be at greater risk. To minimize the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration. (See Dosage and Administration).

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

### **Hypertension:**

NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

### **Heart failure**

Fluid retention and odema have been observed in some patients taking NSAIDs, therefore caution is advised in patients with fluid retention or heart failure.

### **Gastrointestinal Events**

Ibuprofen should be used with extreme caution, and at the lowest effective dose, in patients with a history of gastro-intestinal haemorrhage or ulcer since their condition may be exacerbated.

All NSAIDs can cause gastrointestinal discomfort and serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at anytime without warning. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short term therapy is not without risk.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, as well as patients requiring concomitant low dose aspirin, or for other drugs likely to increase gastrointestinal risk (see INTERACTIONS WITH OTHER MEDICINES).

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, eg. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about signs and symptoms of serious gastrointestinal toxicity

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

### **Severe Skin Reactions**

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

### **Asthma**

Caution is required if ibuprofen is administered to patients suffering from, or with a previous history of, bronchial asthma since ibuprofen has been reported to cause bronchospasm in such patients.

### **Ophthalmological Monitoring**

Adverse ophthalmological effects have been observed with nonsteroidal anti-inflammatory agents; accordingly, patients who develop visual disturbances during treatment with ibuprofen should have an ophthalmological examination.

### **Impaired Liver Function or a History of Liver Disease**

Patients with impaired liver function or a history of liver disease who are on long term ibuprofen therapy should have hepatic function monitored at regular intervals. Ibuprofen has been reported to have a minor and transient effect on liver enzymes.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though rare, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If abnormal liver tests persist or worsen, or if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), ibuprofen should be discontinued.

### **Impaired Renal Function**

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration.

The two major metabolites of ibuprofen are excreted mainly in the urine and impairment of renal function may result in their accumulation. The significance of this is unknown. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to cause nephrotoxicity in various forms; interstitial nephritis, nephrotic syndrome and renal failure. In patients with renal, cardiac or hepatic impairment, those taking diuretics and ACE Inhibitors, and the elderly, caution is required since the use of nonsteroidal anti-inflammatory drugs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored in these patients.

### **Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics:**

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist, an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

### **Aseptic Meningitis**

Aseptic meningitis has been reported only rarely, usually but not always in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

### **Haematological Monitoring**

Blood dyscrasias have been rarely reported. Patients on long term therapy with ibuprofen should have regular haematological monitoring.

### **Coagulation Defects**

Like other non-steroidal anti-inflammatory drugs, ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy.

### **Masking Signs of Infection**

As with other drugs of this class, ibuprofen may mask the usual signs of infection.

### **Special Precautions**

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

### **Use in Pregnancy: (Category C)**

Nonsteroidal anti-inflammatory drugs inhibit 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 delay labour and birth. Continuous treatment with nonsteroidal anti-inflammatory drugs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

### **In Labour and Delivery**

Administration of ibuprofen is not recommended during labor and delivery. The onset of labor may be delayed and the duration increased with a greater bleeding tendency in both mother and child.

### **Use in Lactation**

Ibuprofen is not recommended for nursing mothers.

### **Ability to drive and use machines**

No adverse effects known.

### **Interactions with other medicines**

Care should be taken in patients treated with anti-coagulants, such as warfarin, due to an enhanced effect of anti-coagulants.

Concurrent use of NSAIDs and warfarin has been associated with severe sometimes fatal haemorrhage. The mechanism of this interaction is not known but may involve increased bleeding from NSAID-induced gastrointestinal ulceration or an additive effect of NSAID inhibition of platelet function with the anticoagulant effect of warfarin.

Brufen should only be used in patients taking warfarin if absolutely necessary. Patients taking this combination must be closely monitored.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding

Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides

Ibuprofen has been shown to decrease the renal clearance and increase plasma concentrations of lithium. Lithium plasma concentrations should be monitored in patients on concurrent ibuprofen therapy.

Ibuprofen like other NSAIDs can reduce the antihypertensive effect of ACE inhibitors and beta-blockers with possible loss of blood pressure control and can attenuate the natriuretic effects of thiazide diuretics and furosemide. Diuretics can also increase the risk of nephrotoxicity of NSAIDs. The combined use of the three classes of drugs, thiazides, an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist and an anti-inflammatory drug (NSAID or COX-2 inhibitor) all at the same time increases the risk of renal impairment (see PRECAUTIONS).

NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma cardiac glycoside levels. Care should therefore be taken in patients treated with cardiac glycosides.

Corticosteroids: Increased risk of gastrointestinal bleeding.

Herbal Extracts: Ginkgo biloba may potentiate the risk of bleeding with NSAIDs

Other analgesics: Avoid concomitant use of two or more NSAIDs, including aspirin and cyclooxygenase-2 (COX-2) selective inhibitors, because of the potential of increased adverse effects. Ibuprofen antagonizes the irreversible inhibition of platelet cox-1 induced by low dose aspirin. To reduce this effect, ibuprofen should be administered at least 8 hours before or 30 minutes after taking low dose aspirin.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see PHARMACOLOGY).

Cyclosporine or Tacrolimus: Increased risk of nephrotoxicity when used with NSAIDs .

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.

Zidovudine: Increased risk of hematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of hemarthroses and hematoma in HIV(+) hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

NSAIDs inhibit tubular secretion of methotrexate in animals. As a result, reduction of clearance of methotrexate may occur. Use of high doses of methotrexate concomitant with NSAIDs should be avoided. At low doses of methotrexate caution should be used if ibuprofen is administered concomitantly.

## ADVERSE REACTIONS

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of non-specific allergic reaction and anaphylaxis, respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnea, or assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and very rarely, bullous dermatoses (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme).

### **More common reactions: (greater than 1%)**

#### ***Gastrointestinal:***

The most frequent types of adverse reaction occurring with ibuprofen is gastrointestinal. Gastrointestinal complaints include nausea, epigastric pain, heartburn, diarrhoea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence).

#### ***Auditory and vestibular:***

Tinnitus.

#### ***Cardiovascular:***

Oedema, fluid retention; fluid retention generally responds promptly to discontinuation of the drug.

#### ***Central nervous system:***

Dizziness, headache, nervousness.

#### ***Dermatological:***

Rash (including maculopapular type), pruritus.

#### ***General:***

Decreased appetite.

### **Less common reactions: (less than 1%)**

#### ***Central nervous system:***

Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma.

#### ***Dermatological:***

Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia

#### ***Gastrointestinal:***

Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal haemorrhage, melaena, haematemesis, ulcerative stomatitis, pancreatitis, gastritis, hepatitis, jaundice, abnormal liver function tests.

### ***Haematological***

Neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia and decrease in haemoglobin and haematocrit.

### ***Ocular:***

Amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision) have occurred but is usually reversed after cessation of therapy. Any patient with eye complaints should have an ophthalmological examination which includes central vision fields (see PRECAUTIONS).

### ***Allergic:***

Syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis, bronchospasm.

### **Precise Incidence Unknown (but less than 1%) Causal Relationship Unknown**

### ***Central Nervous System:***

Paraesthesias, hallucinations, dream abnormalities, vertigo

### ***Dermatological:***

Toxic epidermal necrolysis, photoallergic skin reactions

### ***Special Senses:***

Conjunctivitis, diplopia, optic neuritis, cataracts

### ***Haematological:***

Bleeding episodes (eg epistaxis, menorrhagia)

### ***Metabolic/endocrine:***

Gynaecomastia, hypoglycaemic reaction, acidosis

### ***Renal***

Renal nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

### ***Hepatic***

Abnormal liver function, hepatic failure, hepatitis and jaundice.

### ***Cardiovascular***

Arrhythmias (sinus tachycardia, sinus bradycardia)

### ***Allergic***

Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema

### **Additional Post-Marketing Adverse Reactions**

Adverse reactions have been reported during post-approval use of Brufen. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Brufen exposure.

### ***Gastrointestinal***

Exacerbation of colitis and Crohn's Disease (see Contraindications section). Pancreatitis has been reported very rarely.

## **DOSAGE AND ADMINISTRATION**

After assessing risk/benefit ratio in each individual patient, the lowest effective dose for the shortest duration should be used.

Do not halve the tablets.

### **Adult**

The recommended initial dosage of Brufen is 1200 mg - 1800 mg daily in divided doses. Some patients can be maintained on 600 - 1200 mg daily. In severe or acute conditions it can be advantageous to increase the dosage until the acute phase is brought under control, providing that the total daily dosage does not exceed 2400 mg in divided doses.

### **Primary dysmenorrhoea**

The initial dose is 400-800 mg at the first sign of pain or menstrual bleeding, then 400 mg 4-6 hourly with a maximum total daily dose of 1,600 mg.

### **Children**

The daily dosage of Brufen is 20 mg per kg of body weight in divided doses. In juvenile rheumatoid arthritis up to 40 mg per kg of body-weight in divided doses may be taken. In children weighing less than 30 kg the total dose given in 24 hours should not exceed 500 mg.

### **Maintenance dose**

In all indications the dose should be adjusted for each patient and the smallest dose that results in acceptable control of the symptoms employed. In general, patients with rheumatoid arthritis and osteoarthritis tend to require higher doses than patients with other conditions.

### **Geriatric**

In elderly patients receiving 600 - 1,200mg daily ibuprofen appeared to be well tolerated. However, since elderly patients may have a degree of impaired liver or renal function the adult dosage should be used with caution.

### **Impaired Liver Function**

Ibuprofen should be used with caution in patients with impaired liver function (see PRECAUTIONS).

### **Impaired Renal Function**

Ibuprofen should be used with caution in patients with impaired renal function (see PRECAUTIONS).

## OVERDOSAGE

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.

For advice on the management of overdose please contact the Poisons Information centre. In Australia please call 13 11 26 and in New Zealand 0800 764 766.

## PRESENTATION AND STORAGE CONDITIONS

Tablets, 600 mg (white, pillow-shaped, film-coated tablet).  
Tablets, 400 mg (white, pillow-shaped, film-coated tablet).  
Tablets, 200mg (white, pillow-shaped, film-coated tablet).  
Do not halve the tablets.

Contains Lactose.

Store below 25°C.  
Protect from moisture

## MEDICINE CLASSIFICATION

Brufen 200mg - Pharmacy-Only Medicine  
- Prescription Medicine (500 pack size only)

Brufen 400mg, 600mg - Prescription Medicine.

## PACKAGE QUANTITIES

Brufen 200mg	100*, 500's* (bottle) 30*, 40*, 60*, 500's* (blister pack)
Brufen 400 mg	10, 20, 50 (bottle)* 30, 40*, 60*, 500's* (blister pack)
Brufen 600 mg	100 (bottle)* 30, 40*, 60*, 500's* (blister pack)

\* Not currently marketed in New Zealand.

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## **DATE OF PREPARATION**

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