AUSTRALIAN PRODUCT INFORMATION

BRUFEN®

(Ibuprofen) tablets

1 NAME OF THE MEDICINE

Ibuprofen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of ibuprofen as the active ingredient.

Excipients with known effect: sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

White, pillow-shaped, film-coated tablet.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Adults and children 12 years and over

The recommended initial dose of ibuprofen is 400 mg three to four times daily (1,200-1,600 mg per day) with food or fluids. The dose may be taken on an empty stomach. It is recommended that patients with sensitive stomachs take ibuprofen with food.

For acute exacerbations of rheumatoid arthritis and osteoarthritis in patients already on treatment with ibuprofen, a maximum daily dosage of 2,400 mg (800 mg three times daily) may be prescribed, reverting to a maximum of 1,600 mg (400 mg four times daily) daily once the patient is stabilised.

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.

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.

Elderly Population

In elderly patients receiving 600 - 1,200 mg 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.

Tablet Formulation

Take ibuprofen tablets with plenty of fluid. Ibuprofen tablets should be swallowed whole and not chewed, broken, crushed or sucked on to avoid oral discomfort and throat irritation.

Impaired Liver Function

Ibuprofen should be used with caution in patients with impaired liver function (see Section 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Impaired Renal Function

Ibuprofen should be used with caution in patients with impaired renal function (see Section 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cardiovascular

Patients on long term treatment should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

Pregnancy

See Section 4.3 CONTRAINDICATIONS and 4.6 FERTILITY, PREGNANCY AND LACTATION.

4.3 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.

History or active gastrointestinal bleeding or perforation related to previous NSAID therapy.

History or active, ulcerative colitis, Crohn’s disease, recurrent peptic ulceration or gastrointestinal haemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding).

Severe heart failure (NYHA IV).

Patients with severe hepatic impairment.

Treatment of perioperative pain in setting of coronary artery bypass surgery (CABG).

Severe renal failure (glomerular filtration below 30 mL/min).

Conditions involving an increased tendency or active bleeding.

Third trimester of pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Pregnancy).

Lactation (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General Precautions

Prolonged use of any painkillers may induce headaches, which must not be treated with increased doses of the painkillers, including ibuprofen.

Through concomitant consumption of alcohol, NSAID-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Cardiovascular Thrombotic Events

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) or increased duration of use, may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk. 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.

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Physicians and patients should remain alert for such CV events, even in the absence of previous CV symptoms. Patients should be informed about signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

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 oedema 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 peptic ulceration and other gastrointestinal disease 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, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available. These adverse events can occur at any time without warning or a previous history of serious gastrointestinal events. 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

The concomitant administration of ibuprofen and other NSAIDs, including cyclooxygenase-2 (Cox-2) selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. 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.

Caution should be exercised in patients receiving concomitant medication which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin re-uptake inhibitors or antiplatelet drugs such as aspirin (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (see Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)) 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. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. 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.

Severe skin infections and soft-tissue complications may occur in patients with a varicella infection. The role of NSAIDs in the worsening of these infections is uncertain, therefore it is advisable to avoid the use of ibuprofen in known or suspected cases of varicella.

Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)

DRESS has been reported in patients taking NSAIDs. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue the NSAID and evaluate the patient immediately.

Infections and Infestations

Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of Ibuprofen the patient is therefore recommended to go to a doctor without delay.

Respiratory Disorders

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

Ophthalmological Effects

Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who develop visual disturbances during treatment with ibuprofen should have an ophthalmological examination.

Impaired Liver Function or a History of Liver Disease

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.

Physicians and patients should remain alert for hepatoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms) and the steps to take should these signs and/or symptoms occur. 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 NSAIDs. 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. There is a risk of renal impairment especially in dehydrated children, adolescents and in the elderly.

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. 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 NSAIDs may result in deterioration of renal function. The long-term concomitant intake of similar analgesics further increases the risk. For patients with renal, hepatic or cardiac impairment, use the lowest effective dose, for the shortest possible duration and monitor renal function especially in long term treated 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 NSAIDs, 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.

Lactose monohydrate

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.

Use in the Elderly

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

Paediatric Use

No data available.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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, angiotensin II-receptor antagonists and beta-blockers with possible loss of blood pressure control and can attenuate the natriuretic effects of diuretics. Diuretics can also increase the risk of nephrotoxicity of NSAIDs. The combined use of the three classes of drugs, diuretics, 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

Colestyramine: The concomitant administration of ibuprofen and colestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown**.**

Corticosteroids: Increased risk of gastrointestinal ulceration or 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 competitively inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when a single daily dose of ibuprofen 400mg was given within 8 hours before or within 30 minutes after immediate release aspirin (81mg), and when multiple daily doses of ibuprofen 400mg are given with aspirin, a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of this data to the clinical situation the possibility that regular, long term use of ibuprofen may reduce the cardio-protective effect of aspirin cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use.

Ciclosporin 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.

Sulfonylureas: NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of hemarthroses and hematoma in HIV(+) haemophiliacs 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.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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)

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. The risk is believed to increase with dose and duration of therapy. 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.

Oligohydramnios and Neonatal Renal Impairment

Use of NSAIDs from about 20 weeks gestation may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.

Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If, after careful consideration of alternative treatment options for pain management, NSAID treatment is necessary from about 20 weeks, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with NSAIDs if oligohydramnios occurs.

Use in Labour and Delivery

Administration of ibuprofen is not recommended during labour and delivery. The onset of labour 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 use in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Following treatment with ibuprofen, the reaction time of patients may be affected. This should be taken into account where increased vigilance is required, e.g. when driving a car or operating machinery. For information regarding concomitant consumption with alcohol, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – General Precautions.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following adverse reactions possibly related to ibuprofen displayed by MedDRA frequency convention and system organ classification. Frequency groupings are classified according to the subsequent conventions: very common (≥ 10%), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000) and Not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Uncommon	Rhinitis
	Rare	Meningitis aseptic (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia
Immune system disorders	Uncommon	Hypersensitivity
	Rare	Anaphylactic reaction
Psychiatric disorders	Uncommon	Insomnia, anxiety
	Rare	Depression, confusional state
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Paraesthesia, somnolence
	Rare	Optic neuritis
Eye disorders	Uncommon	Visual impairment
	Rare	Toxic optic neuropathy
Ear and labyrinth disorders	Uncommon	Hearing impaired, tinnitus, vertigo
Respiratory, thoracic and mediastinal disorders	Uncommon	Asthma, bronchospasm, dyspnoea
Gastrointestinal disorders	Common	Dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melaena, hematemesis, ulcerative stomatitis, gastrointestinal haemorrhage
	Uncommon	Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation
	Very rare	Pancreatitis
	Not known	Exacerbation of colitis and Crohn's disease
Hepatobiliary disorders	Uncommon	Hepatitis, jaundice, hepatic function abnormal
	Very rare	Hepatic failure
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Urticaria, purpura, angioedema, photosensitivity reaction
	Very rare	Severe forms of skin reactions (e.g. erythema multiforme, bullous reactions including Stevens-Johnson Syndrome and toxic epidermal necrolysis)

	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute Generalised Exanthematous Pustulosis (AGEP), fixed eruption
Renal and urinary disorders	Uncommon	Nephrotoxicity in various forms, e.g. tubulointerstitial nephritis, nephrotic syndrome and renal failure
General disorders and administration site conditions	Common	Fatigue
	Rare	Oedema
Cardiac disorders	Very rare	Cardiac failure, myocardial infarction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Vascular disorders	Very rare	Hypertension

Precise Incidence Unknown (but greater than 1%) Causal Relationship Unknown

Gastrointestinal: Epigastric pain, heartburn, abdominal distress, abdominal cramps and bloating.

Auditory and vestibular: Tinnitus, hearing impaired.

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

Central nervous system: Nervousness.

Dermatological: Pruritus.

General: Decreased appetite.

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

Central nervous system: Emotional lability, somnolence, hallucinations and dream abnormalities.

Dermatological: Alopecia.

Gastrointestinal: Abnormal liver function tests.

Haematological: 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Visual impairment and toxic neuropathy have also been reported.

Allergic: Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis and chills.

Special Senses: Conjunctivitis, diplopia and cataracts.

Haematological: Bleeding episodes (e.g. epistaxis, menorrhagia).

Metabolic/endocrine: Gynaecomastia, hypoglycaemic reaction, acidosis.

Cardiovascular: Arrhythmias (sinus tachycardia, sinus bradycardia).

Post-marketing experience

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 Section 4.3 CONTRAINDICATIONS). Pancreatitis has been reported very rarely.

Skin and subcutaneous tissue disorders: Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)

A causal association for the following adverse effects has not yet been established however they could not be excluded as a possible class-effect:

Pregnancy, puerperium and perinatal conditions: Oligohydramnios, neonatal renal impairment

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults. However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400 mg/kg or greater.

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours.

The most frequently reported symptoms of overdose include nausea, abdominal pain, vomiting, lethargy and drowsiness. Central nervous system (CNS) effects including headache, tinnitus, dizziness, convulsion and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnea and depression of the CNS and respiratory system have also been rarely reported. Cardiovascular toxicity, including hypotension, bradycardia and tachycardia, has been reported. In cases of significant overdose, renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other drugs are being taken.

There is no specific antidote to ibuprofen. Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. If necessary, serum electrolyte balance should be corrected.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

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.

The bioavailability of ibuprofen from one "Brufen 400 mg" tablet is equivalent to that from two "Brufen 200 mg" tablets.

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 the drug enters the CSF or is excreted in breast milk.

99% of ibuprofen is protein bound. The high protein binding of the drug 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), and 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 800 mg ibuprofen as a single dose. After 14-24 hours the plasma levels of drug and metabolites were less than 0.25 micrograms/mL.

Excretion

The kidney is the major route of excretion. 95% of the drug 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).

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, colloidal anhydrous silica, sodium lauryl sulfate, magnesium stearate, hypromellose, purified talc and titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in PVC/PVDC/Al or PVC/Al blister packs containing 10, 30, 40, or 60 tablets.

Some pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutical Goods (ARTG)

AUST R 80659 - BRUFEN ibuprofen 400mg tablet blister pack

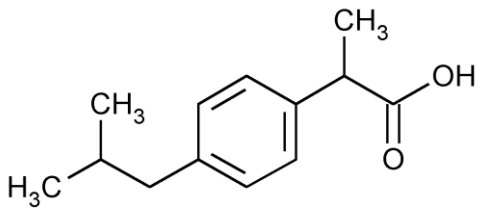
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

The structural formula for ibuprofen is shown below:



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.

CAS Number

15687-27-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

12/11/2001

10 DATE OF REVISION

26/03/2025

Summary Table of Changes

Section Changed	Summary of New Information
4.4	Minor editorial changes
4.8	Addition of ADR fixed eruption with the frequency unknown under 'Skin and subcutaneous tissue disorders'

BRUFEN® is a Viatris company trade mark

BRUFEN_pi\Mar25/00 (CCDS 15-Jan-2025)