

DATA SHEET

BRUFEN[®] SUSTAINED RELEASE (SR)

NAME OF MEDICINE

Ibuprofen 800mg

DESCRIPTION

Ibuprofen is a (\pm)-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.

Brufen SR contains the following inactive ingredients: xanthan gum, povidone, stearic acid, colloidal anhydrous silica, hypromellose, purified talc and opaspray white M-1-7111B.

PHARMACOLOGY

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that possesses analgesic and antipyretic activities. Its mode of action, like that of other NSAIDs, 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

The sustained release form of ibuprofen is formulated to allow a gradual release of the active substance from the gel matrix. Ibuprofen diffuses through an outer gel layer which erodes allowing the aqueous medium to penetrate further into the core. The sustained absorption phase that results provides prolonged plasma levels of ibuprofen in the systemic circulation, reducing the dosage frequency normally required for a drug with a plasma half life of about two hours.

The mean plasma profile of two sustained release 800mg tablets compared to one conventional release 400mg tablet taken four times daily, showed that the sustained release formulation reduced the peaks and troughs characteristic of the conventional release tablets and produced higher mean plasma levels at 5, 10 and 15 hours and, notably at 24 hours. The area under the plasma concentration/time curve for two sustained release tablets was almost identical to that of four conventional release 400mg tablets.

There was no evidence of dose dumping with sustained release ibuprofen. In a study to compare the effects of age there was no major difference between young and elderly age groups. Steady state was reached within one day and there was no evidence of accumulation following repeat dose.

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 (immediate release tablet) 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. In research done with immediate release formulation, 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).

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).

Ibuprofen is contraindicated in patients with severe liver failure.

Ibuprofen is contraindicated in patients with severe renal failure (glomerular filtration below 30 mL/min).

Ibuprofen should not be given to patients with conditions involving an increased tendency to bleeding.

Ibuprofen is contraindicated during the third trimester of pregnancy.

Pregnancy - see **PRECAUTIONS - Use in Pregnancy**

Lactation - see **PRECAUTIONS - 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 oedema have been reported in association with ibuprofen, therefore, the drug should be used with caution in patients with a history of heart failure or hypertension.

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).

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 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.

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 INTERACTIONS WITH OTHER MEDICINES).

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 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

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.

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 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.

Withdrawal of Concomitant Steroid Therapy

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)

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. 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 labor.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy.

Use 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.

Female 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.

Effect on Ability to Drive or Operate Machinery

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.

Interactions with Other Medicines

Food

No information available.

Alcohol

No information available.

Anticoagulants

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

Lithium

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.

Cardiac Glycosides

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.

Cholestyramine

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

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.

Methotrexate

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.

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 hypoglycemia in patients on sulfonylurea medications receiving ibuprofen.

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.

Others

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 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 PRECAUTIONS).

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.

Laboratory Tests

There is no evidence so far that ibuprofen interferes with laboratory tests.

ADVERSE REACTIONS

Hypersensitivity

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) 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).

Gastrointestinal

The most commonly observed adverse events are gastrointestinal in nature. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis and gastrointestinal haemorrhage and exacerbation of colitis and Crohn's disease (see Contraindications section) have been reported following ibuprofen administration. Pancreatitis has been reported very rarely.

Less frequently, gastritis, duodenal ulcer, gastric ulcer and gastrointestinal perforation have been observed.

Cardiovascular

Oedema has been reported in association with ibuprofen treatment.

Other adverse events reported less commonly and for which causality has not necessarily been established include:

Renal

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

Hepatic

Abnormal liver function, hepatic failure, hepatitis and jaundice.

Neurological and special senses

Visual disturbances, visual impairment, toxic neuropathy, optic neuritis, headaches, paraesthesia, anxiety, depression, insomnia, confusion, hallucinations, tinnitus, hearing impaired, vertigo, dizziness, malaise, fatigue and drowsiness.

Haematological

Thrombocytopenia, leucopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Dermatological

Photosensitivity (see Hypersensitivity for other skin reactions)

General

Decreased appetite, fatigue.

DOSAGE AND ADMINISTRATION

These tablets are not capable of providing a divided dose. Do not halve the tablets.

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

Adult

The recommended daily dosage is two Brufen SR tablets taken as a single dose, preferably in the early evening. The tablets should be swallowed whole with plenty of fluids.

In severe or acute conditions, the total daily dosage may be increased to three tablets taken as two tablets in the early evening and an additional tablet in the morning.

Children

Brufen SR is not recommended for children under 12 years.

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 New Zealand 0800 764 766.

PRESENTATION AND STORAGE

Tablets 800mg (white, pillow-shaped, film coated tablet)

These tablets are not capable of providing a divided dose. Do not halve the tablets.

Store below 25°C.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

Brufen SR 800mg - 60's (bottle)*

- 30, 40*, 60* and 500's* (blister pack)

* Not currently marketed.

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