

BRUFEN®



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## 1. Product Name

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BRUFEN 200 mg film coated tablet.

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## 2. Qualitative and Quantitative Composition

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Each film coated tablet contains 200 mg of ibuprofen.

For the full list of excipients, see section 6.1.

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## 3. Pharmaceutical Form

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BRUFEN is a white, circular, biconvex, film coated tablet, with "IBU 200" embossed on one side and plain on the other side.

Do not halve tablets.

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## 4. Clinical Particulars

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### 4.1 *Therapeutic indications*

BRUFEN is effective in the temporary relief of pain and/or inflammation associated with:

- Headache
- Migraine headache
- Tension headache
- Dental pain
- Backache
- Muscular pain
- Period pain
- Arthritic pain
- Sinus pain
- Cold and flu symptoms.

Reduces fever.

### 4.2 *Dose and method of administration*

#### **Dose**

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

#### ***Adults and children from 12 years***

2 tablets, then 1-2 tablets every 4 hours as necessary (maximum 6 tablets in 24 hours).

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### **Children (7 to 12 years)**

1 tablet every 6 to 8 hours as necessary (maximum 4 tablets in 24 hours).

BRUFEN should not be used for more than 3 days at a time, except on medical advice.

Do not give BRUFEN to children under 7 years.

### **Method of administration**

In order to achieve faster onset of action, the dose may be taken on an empty stomach. It is recommended that patients with sensitive stomachs take ibuprofen with food.

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

### **4.3 Contraindications**

- Known hypersensitivity to ibuprofen or any of the excipients listed in section 6.1.
- Hypersensitivity (e.g. asthma, rhinitis or urticaria) to aspirin or other non-steroidal anti-inflammatory drugs.
- History of gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- Active or history of 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).
- Severe liver failure.
- Severe renal failure (glomerular filtration below 30 mL/min).
- Conditions involving an increased tendency or active bleeding.
- During the third trimester of pregnancy.

### **4.4 Special warnings and precautions for use**

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 and thrombotic events**

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day), may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen ( $\leq$  1200 mg/day) is associated with an increased risk of arterial thrombotic events.

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 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.

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 the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives 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 medicine 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 any time 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 section 4.5).

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).

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..

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).

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

When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity

## **Severe skin reactions**

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. Patients appear to be at highest risk of these reactions early in the course of therapy. In the majority of cases, the onset of the reaction occurs within the first month of treatment. Acute generalized exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

In exceptional cases, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of ibuprofen in case of varicella.

### **Infections and infestations**

Exacerbation of skin 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, urticaria or angioedema in such patients.

### **Allergic reactions**

Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed rarely. At the first signs of hypersensitivity reaction after taking/administering ibuprofen, therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Caution is required in patients who have had hypersensitivity or allergic reactions to other substances, as they could be at an increased risk of hypersensitivity reactions occurring with ibuprofen.

Caution is required in patients who suffer from hayfever, nasal polyps or chronic obstructive respiratory disorders as an increased risk exists for them of allergic reactions occurring. These may present as asthma attacks (so-called analgesic asthma), Quincke's edema or urticaria.

### **Ophthalmological effects**

Adverse ophthalmological effects have been observed with non-steroidal anti-inflammatory agents. Any patient who develops 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. There is a risk of renal impairment especially in dehydrated elderly, children and adolescents.

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. Non-steroidal anti-inflammatory agents 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 non-steroidal anti-inflammatory agents may result in deterioration of renal function.

The long term concomitant intake of various 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.

### **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.

### **Elderly population**

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

## **4.5 Interaction with other medicines and other forms of interaction**

### **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 hemorrhage. 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 anticoagulant effect of warfarin.

Ibuprofen 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 with anti-platelet agents (e.g. clopidogrel & ticlopidine) and selective serotonin reuptake inhibitors (SSRIs).

## **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 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 single doses of ibuprofen 400 mg were taken within 8 hours before, or within 30 minutes after immediate release aspirin (81 mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

## **Ciclosporin or tacrolimus**

Increased risk of nephrotoxicity when used with NSAIDs.

## **Mifepristone**

A decrease in the efficacy of the medicinal product can theoretically occur due to the anti-prostaglandin properties of NSAIDs including acetylsalicylic acid. Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy.

## **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, 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).

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, betablocker or angiotensin-II antagonist and agents that inhibit cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

## **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.

## **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**

### **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 labor.

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

### **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.

### **Breast-feeding**

In the limited studies so far available, ibuprofen appears in the breast milk in very low concentrations. Ibuprofen is not recommended for use in nursing mothers.

### **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.

There is some evidence that drugs which inhibit cyclooxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

## **4.7 Effects on ability to drive and use machines**

Following treatment with ibuprofen, the reaction time of patients may be affected. Care should be taken when driving or operating machinery as the activity may be affected by dizziness, drowsiness, fatigue and visual disturbance. This applies to a greater extent in combination with alcohol.

## **4.8 Undesirable effects**

The pattern of adverse events reported for ibuprofen is similar to that for other NSAIDs.

### ***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 section 4.3) have been reported following ibuprofen administration.

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



## Immune system disorders

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, erythema multiforme, bullous dermatoses (including Stevens-Johnson syndrome and toxic epidermal necrolysis).

## Skin and subcutaneous tissue disorders

In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see section 4.4).

## Cardiac and vascular disorders

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg / day) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

The following adverse reactions possibly related to ibuprofen are displayed by MedDRA frequency convention and system organ classification. Frequency groupings are classified according to the subsequent conventions: very common ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $<1/10$ ), Uncommon ( $\geq 1/1,000$  to  $<1/100$ ), Rare ( $\geq 1/10,000$  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	Aseptic meningitis (see section 4.4)
Blood and lymphatic system disorders	Rare	Thrombocytopenia, leucopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia  First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising
Immune system disorders	Uncommon	Hypersensitivity
	Rare	Anaphylactic reaction  Symptoms could be: facial, tongue and laryngeal swelling, dyspnea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock)
Psychiatric disorders	Uncommon	Insomnia, anxiety
	Rare	Depression, confusional state
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Paraesthesia, somnolence
	Rare	Optic neuritis

System organ class	Frequency	Adverse reaction
	Not known	Hallucinations, malaise, and drowsiness
Eye disorders	Uncommon	Visual impairment
	Rare	Toxic optic neuropathy
Ear and labyrinth disorders	Uncommon	Tinnitus, hearing impaired, vertigo
Respiratory, thoracic and mediastinal disorders	Uncommon	Asthma, bronchospasm, dyspnoea
Gastrointestinal disorders	Common	Dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melena, hematemesis, 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	Abnormal liver function, hepatitis, jaundice.
	Very rare	Hepatic failure
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Urticaria, pruritus, 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	DRESS (Drug reaction with eosinophilia and systemic symptoms)  AGEP (Acute Generalized Exanthematous Pustulosis)
Renal and urinary disorders	Uncommon	Renal nephrotoxicity in various forms, including tubulointerstitial nephritis, nephrotic syndrome and renal failure.
General disorders and administration site conditions	Common	Fatigue.
	Rare	Oedema
	Not known	Decreased appetite,

System organ class	Frequency	Adverse reaction
Cardiac disorders	Very rare	Cardiac failure, myocardial infarction (see section 4.4)
	Not known	Stroke.
Vascular disorder	Very rare	Hypertension.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

## 4.9 Overdose

### Toxicity

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.

### Symptoms

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, vomiting, abdominal pain, lethargy and drowsiness. Central nervous system (CNS) effects include headache, tinnitus, dizziness, convulsion and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea 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.

### Treatment

There is no specific antidote for ibuprofen overdose. 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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

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## 5. Pharmacological Properties

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### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non-steroidal, ATC code: M01AE01.

#### Pharmacodynamic effects

Ibuprofen is a propionic acid derivative non-steroidal anti-inflammatory agent with analgesic, anti-inflammatory and anti-pyretic effects. The medicine's therapeutic effects are thought to result from its inhibitory effect on the enzyme cyclooxygenase, which results in a marked reduction in prostaglandin synthesis. These properties provide symptomatic relief of inflammation, pain and fever.

## **Clinical efficacy and safety**

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 single doses of ibuprofen 400 mg were taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid/aspirin cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

## **5.2 Pharmacokinetic properties**

Ibuprofen is a racemic mixture of [+]S- and [-]R-enantiomers.

### **Absorption**

Ibuprofen is rapidly absorbed from the gastrointestinal tract with a bioavailability of 80-90%. Peak serum levels occur one to two hours after administration of immediate release formulations.

Studies including a standard meal show that food does not markedly affect total bioavailability.

### **Distribution**

Approximately 99% of ibuprofen is protein bound. Ibuprofen has a small volume of distribution being about 0.12-0.2L/kg in adults.

### **Biotransformation**

Ibuprofen is rapidly metabolized in the liver through cytochrome P450, preferentially CYP2C9, to two primary inactive metabolites, 2-hydroxyibuprofen and 3-carboxyibuprofen. Following oral ingestion of the drug, slightly less than 90% of an oral dose of ibuprofen can be accounted for in the urine as oxidative metabolites and their glucuronic conjugates. Very little ibuprofen is excreted unchanged in the urine.

### **Elimination**

Excretion via the kidney is rapid and complete.

The elimination half-life of immediate release formulations is approximately 2 hours. The excretion of ibuprofen is virtually complete 24 hours after the last dose.

## **Special populations**

### ***Elderly***

Given that no renal impairment exists, there are only small, clinically insignificant differences in the pharmacokinetic profile and urinary excretion between the young and the elderly.

### ***Paediatric population***

The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5 mg/kg to 10 mg/kg bodyweight) in children aged 1 year or over, appears similar to that in adults. Children 3 months to 2.5 years appeared to have a higher volume of distribution (L/kg) and clearance (L/kg/h) of ibuprofen than did children >2.5 to 12 years of age.

### ***Renal impairment***

For patients with mild renal impairment, increased plasma level of (S)-ibuprofen, higher AUC values for (S)-ibuprofen and increased enantiomeric AUC (S/R) ratios as compared with healthy controls have been reported. In end-stage renal disease patients receiving dialysis, the mean free fraction of ibuprofen was about 3% compared with about 1% in healthy volunteers. Severe impairment of

renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis (see sections 4.3 and 4.4).

### ***Hepatic impairment***

Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters.

In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) treated with racemic ibuprofen, an average 2-fold prolongation of the half-life was observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of (R)-ibuprofen to the active (S)-enantiomer (see sections 4.3 and 4.4).

### **5.3 *Preclinical safety data***

Refer to sections 4.5 and 4.6 for relevant data.

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## **6. Pharmaceutical Particulars**

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### **6.1 *List of excipients***

BRUFEN tablets contain:

- maize starch,
- colloidal silica anhydrous,
- stearic acid.

The film coating contains:

- hypromellose
- titanium dioxide,
- polyethylene glycol.

BRUFEN tablets are lactose and gluten free.

### **6.2 *Incompatibilities***

Not applicable.

### **6.3 *Shelf life***

2 years.

### **6.4 *Special precautions for storage***

Store below 30°C.

### **6.5 *Nature and contents of container***

Brufen 200 mg Al/PVC blister pack. Pack-sizes of 30, 60 and 100 film-coated tablets.

Not all pack sizes may be marketed.

### **6.6 *Special precautions for disposal***

Not applicable.

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## 7. Medicines Schedule

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Pharmacy Only Medicine.

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## 8. Sponsor Details

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Mylan New Zealand Ltd  
PO Box 11183  
Ellerslie  
AUCKLAND  
Customer Services Freephone: 0800 579 811

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## 9. Date of First Approval

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1 October 2009

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## 10. Date of Revision of the Text

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10 August 2020

Section Changed	Summary of New Information
3	Added "Do not halve tablets." To align with information provided in section 4.2
4.3	Included "Active or" to contraindication of recurrent peptic ulceration or gastrointestinal haemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding).  Minor editorial change (MEC): Spelling of haemorrhage
4.4	MEC: Rearrangement of some text on gastrointestinal bleeding and ulcerations  Included elderly at higher risk of impaired renal function if dehydrated  Revised severe skin reaction precaution, including additional information on AGEP  Addition of warning that elderly have increased frequency of adverse reactions to NSAIDs  Revised cardiovascular and thrombotic information
4.5	Additional information on gastrointestinal bleeding with anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)  Additional information added for patients with compromised renal function and co-administration with an ACE inhibitor, betablocker or angiotensin-II antagonist and agents that inhibit cyclooxygenase
4.6	Additional information added on concentrations of ibuprofen in breast milk.  Information added on impairment of fertility by affecting ovulation

Section Changed	Summary of New Information
4.8	<p>Section revised and updated to tabulated format.</p> <p>Deletion of duplicate ADE visual impairment.</p> <p>Additional information regarding immune system disorders, skin and subcutaneous tissues disorders, gastrointestinal cardiac and vascular disorders</p>
4.9	<p>Revised treatment of overdose to remove gastric lavage and include activated charcoal and symptomatic treatment.</p>
5.1	<p>Removal of chemical characteristics of ibuprofen</p>
5.2	<p>Added Pharmacokinetic data for paediatric population.</p> <p>MEC: correction of referenced sections</p>
6.1	<p>MEC: excipients present in product converted into list.</p>
6.5	<p>Added packaging material and minor editorial changes to harmonise with standard formatting.</p>
8	<p>Sponsor phone number updated.</p>