

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: lactose.

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

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children 12 years and over

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

Do not exceed the recommended dose.

Pregnancy

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

Children under 12 years

BRUFEN PAIN should not be administered to children aged less than 12 years.

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

4.3 CONTRAINDICATIONS

Ibuprofen is contraindicated for use in patients with:

- known hypersensitivity or idiosyncratic reaction to ibuprofen (or any of the inactive ingredients)
- known hypersensitivity to aspirin and other NSAIDs
- asthma that is aspirin or NSAID sensitive
- active gastrointestinal bleeding or peptic ulceration

- renal impairment
- heart failure
- severe liver impairment
- undergoing treatment of perioperative pain in a setting of coronary artery bypass surgery (CABG)

Use of BRUFEN PLUS is contraindicated during the third trimester of pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION).

BRUFEN PLUS should not be taken with other products containing ibuprofen, aspirin, or with other anti-inflammatory medicines or other medicines being taken regularly unless under medical advice.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

BRUFEN PLUS should be used with caution in patients with:

- Previous history of gastrointestinal haemorrhage or ulcers
- Asthma who have not previously taken NSAIDs
- Hepatic, or cardiac impairment

BRUFEN PLUS should be used with caution in:

- Pregnancy (See Section 4.6 FERTILITY, PREGNANCY AND LACTATION)
- Elderly patients (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, USE IN ELDERLY)

BRUFEN PLUS should be taken with caution with other products containing aspirin or salicylates.

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

Refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, for additional information.

Identified precautions

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms. BRUFEN PAIN should not be used for more than 3 days at a time except on medical advice. Treatment should be immediately discontinued at the first appearance of cutaneous reactions or relevant gastrointestinal events.

BRUFEN PAIN should not be taken with other medicines containing ibuprofen, aspirin or other anti-inflammatory medicines or other medicines being taken regularly unless under medical advice.

On prolonged use of any painkillers, headache may occur that must not be treated with increased doses of the medicinal product.

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

Cardiovascular and cerebrovascular effects

Observational studies have indicated that NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk.

Clinical trial and epidemiological data suggest that the use of ibuprofen, particularly at high doses (2400 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events

(for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200 mg daily) is associated with an increased risk of myocardial infarction.

Cases of Kounis syndrome have been reported in patients treated with ibuprofen-containing products. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

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

Fluid retention, hypertension and oedema have been reported in association with NSAID therapy. Patients taking antihypertensives with NSAIDs may have an impaired antihypertensive response.

BRUFEN PAIN tablets should only be used under medical advice in patients with hypertension (see also Section 4.3 CONTRAINDICATIONS – Heart Failure). Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischemic 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.

Gastrointestinal (GI)

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Gastrointestinal GI bleeding, ulceration and perforation which can be fatal, have been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. The frequency of such events may increase with dose or duration of use. Patients at most risk of developing these types of GI complications with NSAIDs are the elderly, patients using concomitant aspirin, patients with a history of, or active GI disease (e.g. ulceration, GI bleeding or inflammatory conditions) and patients with a history of smoking and alcoholism. These patients should commence treatment on the lowest dose available.

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). BRUFEN PAIN should be used only under medical advice in:

- Patients with previous history of GI haemorrhage or ulcers (see also Section 4.3 CONTRAINDICATIONS – Active GI Bleeding or Peptic Ulceration). Patients should report any new or unusual abdominal symptoms during treatment. If GI bleeding or ulceration occurs in patients receiving BRUFEN PAIN, the treatment should be withdrawn immediately. Appropriate clinical evaluation and treatment should be considered.
- Patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin or other NSAIDs including cyclooxygenase-2 (COX-2) selective inhibitors (see Section 4.5 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

Respiratory

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

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 oedema or urticaria.

SLE and mixed connective tissue disease

BRUFEN PAIN should be used with caution in patients with systemic lupus erythematosus and mixed connective tissue disease as there is a risk of increased aseptic meningitis. Although it is probably more likely to occur in patients with these diseases and other related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Skin and subcutaneous tissue disorders

Severe cutaneous adverse reactions (SCARs)

Dermatological effects: Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Drug Reaction with Eosinophilia with Systemic Symptoms (see DRESS), toxic epidermal necrolysis, and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Ibuprofen use should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity and medical advice should be sought immediately. Most of these reactions occurred within the first month. If signs and symptoms suggestive of these reactions appear, BRUFEN PAIN should be withdrawn immediately, and an alternative treatment considered (as appropriate).

Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) may occur with ibuprofen-containing products. The acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localised on the skin folds, trunk and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of BRUFEN PAIN tablets should be discontinued, and appropriate measures taken if needed.

In exceptional cases, varicella can be at the origin of serious cutaneous and soft tissues 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.

Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)

DRESS has been reported in patients using 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.

Masking of symptoms of underlying infections

BRUFEN PAIN can mask symptoms of infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When BRUFEN PAIN is administered for fever or pain relief in relation infection, monitoring of infection is advised. In non-hospital settings the patient should consult a doctor if symptoms persist or worsen (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for additional information).

Use in hepatic impairment

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.

Ibuprofen has been reported to have a minor and transient effect on liver enzymes. Therefore, BRUFEN PAIN tablets should be used with caution in patients with hepatic dysfunction.

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

Renal

Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

Haematological effects

Ibuprofen, like other NSAIDs, can inhibit platelet aggregation and prolong bleeding time in normal subjects.

Use in renal impairment

Renal impairment as renal function may deteriorate.

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 the elderly.

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may cause renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE inhibitors and the elderly. Discontinuation of NSAIDs therapy is usually followed by recovery to the pretreatment state.

Use in the elderly

Ibuprofen should not be taken by adults over the age of 65 without careful consideration of co-morbidities and co-medications because of an increased risk of adverse effects, in particular heart failure, gastro-intestinal ulceration and renal impairment (see also Section 4.3 CONTRAINDICATIONS).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Ibuprofen (like other NSAIDs) should be avoided in combination with:

- **Aspirin:** Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, no clinically relevant effect is considered to be likely for occasional ibuprofen use.
- **Other NSAIDs including aspirin and cyclooxygenase-2-selective inhibitors:** Avoid the use of two or more NSAIDs as this may increase the risk of adverse effects.

The following interactions with ibuprofen have been noted:

- **ACE inhibitors, diuretics and other antihypertensives:** Ibuprofen can reduce the antihypertensive effect of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and beta-blockers with possible loss of blood pressure control and hyperkalaemia. Ibuprofen may reduce the antihypertensive and natriuretic effect of diuretics. Diuretics can 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 cyclooxygenase-2 (COX-2) inhibitor) all at the same time increases the risk of renal impairment. The combination of drugs from these three classes should be used with caution particularly in elderly patients. 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 or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a NSAID concomitantly with ACE inhibitors or angiotensin II antagonists. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.
- **Aminoglycosides:** NSAIDs may decrease the excretion of aminoglycosides.
- **Anticoagulants, including warfarin:** Ibuprofen interferes with the stability of INR and may increase the risk of severe bleeding and sometimes fatal haemorrhage, especially from the gastrointestinal tract. Ibuprofen should only be used in patients taking warfarin if absolutely necessary and they must be closely monitored.
- **Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):** Increased risk of gastrointestinal bleeding.
- **Cardiac glycosides:** Ibuprofen may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma glycoside levels.
- **Cholestyramine:** The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.
- **Ciclosporin:** Increased risk of nephrotoxicity.
- **Corticosteroids:** An increased risk of gastrointestinal ulceration or bleeding may occur with corticosteroids.
- **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.
- **Ginkgo biloba:** Ginkgo may potentiate the risk of bleeding with NSAIDs.
- **Lithium:** Ibuprofen may decrease the renal clearance and increase plasma concentrations of lithium.
- **Methotrexate:** There is potential for an increase in plasma levels of methotrexate. Ibuprofen reduces methotrexate clearance.
- **Mifepristone:** NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
- **Probenecid and phenytoin:** Interactions may also occur with probenecid and phenytoin.
- **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 antidiabetic medicines such as sulfonylureas. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.
- **Tacrolimus:** Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

- **Zidovudine:** Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthrosis and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Lactose

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

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

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

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

Oligohydramnios and Neonatal Renal Impairment

Use of NSAIDs from about 20 weeks gestation may cause neonatal 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.

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 appears in breast milk in very low concentrations. 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. This applies to a greater extent in combination with alcohol.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

- Gastrointestinal-dyspepsia, heartburn, nausea, loss of appetite, stomach pain, diarrhoea.
- Central nervous system (CNS) –dizziness, fatigue, headache, nervousness.
- Hypersensitivity reactions – skin rashes and itching. Rarely exfoliative dermatitis and epidermal necrolysis have been reported with ibuprofen.
- Rare cases of photosensitivity.
- Cardiovascular fluid retention and in some cases oedema. These effects are rare at non-prescription doses.

The frequencies of adverse effects are defined by MedDRA frequency convention and system organ classification as follows:

Very common: $\geq 1/10$

Common: $\geq 1/100$, $< 1/10$

Uncommon: $\geq 1/1,000$, $< 1/100$

Rare: $\geq 1/10,000$, $< 1/1,000$

Very Rare: $< 1/10,000$, including isolated reports.

Not known: Cannot be estimated from the available data

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of:

- a) non-specific allergic reactions and anaphylaxis
- b) respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm, dyspnoea
- c) Assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely bullous dermatoses (including epidermal necrolysis and erythema multiforme)

The following adverse effects relates to those experienced with ibuprofen at OTC doses, for short-term use. In the treatment of chronic conditions, under long term treatment, additional adverse effects may occur.

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

Blood and Lymphatic System Disorders:

Rare: Haematopoietic disorders: Leukopenia, thrombocytopenia, 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.

Very rare: Eosinophilia, reduction of haemoglobin and haematocrit, pancytopenia, reversible platelet aggregation, alveolitis, pulmonary eosinophilia, anaemia.

Hypersensitivity reactions:

Uncommon: Hypersensitivity reactions with urticaria and pruritus.

Rare: Anaphylactic reaction. Symptoms could be facial, tongue and larynx, swelling, dyspnoea, apnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock). This may be characterised by abdominal pain, fever, shivering, nausea and vomiting. Exacerbation of asthma and bronchospasm.

Hepatotoxicity and aseptic meningitis which occur less frequently may also be hypersensitivity reactions.

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

Gastrointestinal disorders:

The most commonly observed adverse events are gastrointestinal in nature.

Common: Abdominal pain, nausea, dyspepsia, diarrhoea, flatulence, constipation, vomiting, melaena, haematemesis (sometimes fatal, particularly in the elderly), gastrointestinal haemorrhage.

Uncommon: Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation.

Rare: Heartburn, loss of appetite, dryness of the mouth.

Very rare: Pancreatitis, duodenitis, oesophagitis, ulcerative stomatitis, gastritis.

Gastric pyrosis. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, gastrointestinal haemorrhage and exacerbation of colitis and Crohn's disease (see Section 4.3 CONTRAINDICATIONS) have been reported following ibuprofen administration. Less frequently, gastritis, duodenal ulcer and gastric ulcer and gastrointestinal perforation have been observed.

Nervous System:

Common: Headache, dizziness.

Uncommon: Paraesthesia, somnolence.

Rare: Optic neuritis.

Very rare: Nervousness, drowsiness, irritability, difficulty in concentrating, emotional instability, convulsions.

General disorders and administration site conditions:

Common: Fatigue.

Rare: Oedema.

Ear and labyrinth disorders:

Uncommon: Tinnitus, hearing impaired, vertigo.

Psychiatric disorders:

Uncommon: Insomnia, anxiety.

Rare: Depression, confusional state.

Renal and Urinary Disorders:

Uncommon: Nephrotoxicity in various forms, e.g. tubulointerstitial nephritis, nephrotic syndrome and renal failure.

Very rare: Papillary necrosis, especially in long-term use, associated with increased serum urea and oedema, hepato-renal syndrome.

Not known: Renal tubular acidosis* (see "Post-Marketing Experience").

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

Metabolism and nutrition disorders

Not known: Hypokalaemia* (see “Post-Marketing Experience”).

Hepatobiliary disorders:

Uncommon: Hepatitis, jaundice, hepatic function abnormal.

Very rare: Liver disorders can occur, especially in long term treatment, including hepatotoxicity, pancreatitis, hepatic necrosis, hepatic insufficiency, hepatic failure.

Skin and Subcutaneous Tissue Disorders:

Common: Rash.

Uncommon: Urticaria, pruritis, purpura, angioedema, photosensitivity reaction.

Rare: Skin peeling, alopecia, exfoliative dermatitis, photosensitive dermatitis, maculopapular, rash.

Very rare: Severe cutaneous adverse reactions (SCARs) (e.g. erythema multiforme, bullous reactions including Stevens-Johnson syndrome, and toxic epidermal necrolysis).

Not known: Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS), Acute generalized exanthematous pustulosis (AGEP), photosensitivity reactions, fixed eruption.

In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and Infestations" and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Immune System Disorders:

In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever, or disorientation have been observed.

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.

Uncommon: Rhinitis.

Rare: Aseptic meningitis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cardiovascular and Cerebrovascular:

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Rare: Cerebrovascular accidents, hypotension, congestive cardiac insufficiency in patients with compromised cardiac function, palpitations.

Very rare: Cardiac failure, myocardial infarction (also see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Not known: Kounis syndrome.

Vascular Disorders:

Very rare: Hypertension

Respiratory, thoracic and mediastinal disorders:

Uncommon: Asthma, bronchospasm, dyspnoea.

Eye Disorders:

Uncommon: Visual impairment.

Rare: Toxic optic neuropathy, dryness of the eyes.

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

Other:

Effect on the endocrine system and on the metabolism.

Post-Marketing Experience

* Metabolism and nutrition disorders, renal and urinary disorders: Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of ibuprofen at higher than recommended doses.

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

In adults the dose response effect is less clear cut than in children where ingestion of more than 400 mg/kg may cause symptoms. The half-life in overdose is 1.5-3 hours.

Symptoms: Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as vertigo, drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning, hyperkalaemia and metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur.

Exacerbation of asthma is possible in asthmatics.

Management: Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 possesses analgesic, antipyretic anti-inflammatory properties, similar to other non-steroid anti-inflammatory drugs (NSAIDs). Its mechanism of action is unknown, but is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthetase inhibition.

Ibuprofen has shown anti-inflammatory, analgesic and antipyretic activity in both animal and human studies. These properties provide symptomatic relief of inflammation and pain in rheumatoid arthritis, osteoarthritis and allied conditions.

Clinical Trials

This information is not available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ibuprofen is well absorbed from the gastrointestinal tract.

Metabolism

It is highly bound (90-99%) to plasma proteins and is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation.

Excretion

Both inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion. The elimination half-life of ibuprofen is in the range of 1.9 to 2.2 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

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

6.5 NATURE AND CONTENTS OF CONTAINER

Available in cartons with PVC/Aluminium blister packs containing 10, 28, 50* tablets.

* Not all pack sizes may be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 401754 – BRUFEN® PAIN ibuprofen 400 mg film-coated tablet blister pack

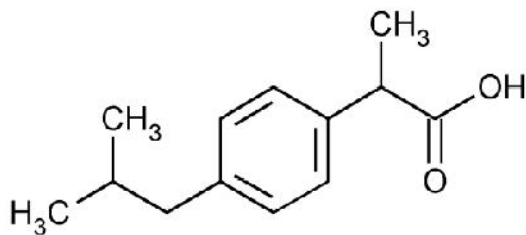
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

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 (< 0.1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone.

Chemical structure:



Chemical formula: C₁₃H₁₈O₂

Molecular weight: 206.3

CAS Number: 15687-27-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S2 – Pharmacy Medicine (10 tablet pack sizes)

S3 – Pharmacist Only Medicine (28 & 50 tablet pack sizes)

8 SPONSOR

Viatrix Pty Ltd

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatrix.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

03/01/2023

10 DATE OF REVISION

16/02/2026

Summary Table of Changes

Section Changed	Summary of New Information
4.2	Addition of lowest effective dose information.
4.3	Addition of aspirin, or other medicines being taken regularly as a contraindication.
4.4	Addition of identified precautions; clinical trial data and Kounis syndrome under Cardiovascular and Cerebrovascular Effects heading; use of BRUFEN PLUS under medical advice in patients with hypertension; renal impairment information; Severe cutaneous adverse reactions (SCARs) under Skin and Subcutaneous Tissue Disorders heading; product specific special warnings information. Addition of headache and alcohol warning; Allergic Reactions heading; gastrointestinal bleeding and perforation in elderly population; added information under Cardiovascular and Cerebrovascular effects; addition of Haematological Effects heading; expansion of Renal Effects information; addition of varicella under Skin and Subcutaneous Tissue Disorders heading, addition of Renal heading with renal tubular acidosis and hypokalaemia information.
4.5	Ibuprofen avoided in combination with aspirin and other NSAIDs; update to ACE inhibitors, diuretics and other antihypertensives; addition of ‘ulceration’ under corticosteroids; an increase in plasma levels of methotrexate to methotrexate; update to zidovudine. Inclusion of hydration consideration with ACE inhibitors; inclusion of, aminoglycosides, cholestyramine, CYP2C9 inhibitors, ginkgo biloba, sulfonylureas.
4.6	Update to ‘Use in pregnancy’ paragraph, inclusion of Labour and Delivery heading and information, update to use in breastfeeding as not recommended.
4.7	Inclusion of information relating to driving a car and operating machinery.
4.8	Update to adverse reactions, frequencies and inclusion of table.
4.9	Update to overdose information. Addition of renal tubular acidosis and hypokalaemia information.

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BRUFEN PAIN_pi\Feb26/00 (CCDS 15-Jan-2025)