NEW ZEALAND DATA SHEET

IBUPROFEN

1. Product Name

IBUPROFEN 200 mg film coated tablet.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 200 mg of ibuprofen.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

IBUPROFEN 200 mg tablets are white, circular, biconvex, film coated tablet, with "IBU 200" embossed on one side and plain on the other side.

Do not halve tablets.

4. Clinical Particulars

4.1 Therapeutic indications

- Rheumatoid arthritis
- Osteoarthritis
- Juvenile rheumatoid arthritis
- Primary dysmenorrhoea
- Pyrexia

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

4.2 Dose and method of administration

Dose

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest duration should be used (see section 4.4).

Adults

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

Primary dysmenorrhoea

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

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.

Special populations

Paediatric

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

Do not give IBUPROFEN film coated tablets to children under 7 years.

Elderly

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

Impaired liver function

Ibuprofen should be used with caution in patients with impaired liver function (see section 4.4).

Impaired renal function

Ibuprofen should be used with caution in patients with impaired renal function (see section 4.4).

Method of administration

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

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

Undesirable effects may be minimized using the lowest effective dose for the shortest duration necessary to control symptoms (see sections 4.2 and GI and cardiovascular risks below).

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

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 (≤ 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 peptic ulceration and other gastrointestinal disease since their condition may be exacerbated (see section 4.3).

Gastrointestinal bleeding, ulceration or perforation has been reported with all NSAIDs at any time during treatment. These adverse events can be fatal and may occur with or without warning symptoms or a previous history of serious gastrointestinal events..

Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, as well as patients requiring concomitant low dose aspirin, or for other drugs likely to increase gastrointestinal risk (see section 4.5).

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.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing ibuprofen doses in patients with a history of ulcers, particularly if complicated with hemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available.

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.

Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) in the initial stages of treatment.

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 disorder

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.

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..

Caution is required in patients with renal, hepatic or cardiac impairment since the use of NSAIDs may result in deterioration of renal function. The habitual concomitant intake of similar painkillers further increases this risk.. For patients with renal, hepatic or cardiac impairment, use the lowest effective dose, for the shortest possible duration (see Section 4.3).

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 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.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. 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

Ibuprofen is contraindicated in 3rd trimester of pregnancy.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and congenital and cardiac malformation and gastroschisis associated with NSAID use 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/fetal 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 the expected benefits to the mother outweigh the risks to the fetus. If there is a compelling need for NSAID treatment for 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.

Use of NSAIDs in the second or third trimester may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Oligohydramnios is generally seen after days to weeks of treatment, although it has been reported as soon as 48 hours after NSAID initiation. Oligohydramnios is usually, but not always, reversible after treatment discontinuation. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with Ibuprofen if oligohydramnios occurs.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may lead to the following:

- Cardiopulmonary toxicity (with premature closure of the fetal ductus arteriosus and pulmonary hypertension)
- Fetal renal impairment, which may progress to renal failure with oligohydramnios
- Inhibition of platelet aggregation, and may delay labour and birth

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).

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 (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 (≥ 1/10), Common (≥ 1/100 to <1/10), Uncommon (≥ 1/1,000 to <1/100), Rare (≥ 1/10,000 to <1/1,000), Very rare (<1/10,000) and Not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Rhinitis.
	Rare	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.
	Not known	Hallucinations, malaise and drowsiness.
Eye disorders	Uncommon	Visual impairment.
	Rare	Toxic optic neuropathy.
Ear and labyrinth disorders	Uncommon	Hearing impaired, tinnitus, vertigo.

System organ class	Frequency	Adverse reaction
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 and 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 disorders	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).

5. Pharmacological Properties

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 drug (NSAID) 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 0.12-0.2 L/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 4.2, 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 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

Refer to sections 4.5 and 4.6 for relevant data.

6. Pharmaceutical Particulars

6.1 List of excipients

Ibuprofen tablets contain:

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

The film coating contains:

- hypromellose,
- titanium dioxide
- polyethylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

IBUPROFEN 200 mg Al/PVC blister pack. Pack size of 20 or 1000 film-coated tablets.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

3 February 2011

10. Date of Revision of the Text

15 August 2022

Summary table of changes

Section Changed	Summary of New Information
4.6	Additional warning information for use of Ibuprofen during pregnancy Minor editorial changes
10	New Date of Revision of Text