

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Brufen Paediatric 100 mg/5 ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 100mg ibuprofen

Excipients with known effect: Each 5ml also contains:

5mg methyl parahydroxybenzoate (E218)
 2.5mg propyl parahydroxybenzoate (E216)
 500mg sorbitol solution non-crystallising (E420)
 3.3 g sucrose
 0.5mg sunset yellow FC edicol (E110)
 12.5mg sodium benzoate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension.

Orange-coloured and flavoured syrup-like suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Brufen Paediatric Oral Suspension is indicated in the management of various arthroses such as rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's Disease) and osteoarthritis, fibrositis, ankylosing and other muscular syndromes such as low back pain, soft tissue trauma and various inflammations of tendon, joint capsules and ligaments.

As an analgesic in the relief of mild to moderate pain.

Ibuprofen is indicated for the treatment of pyrexia in children.

4.2 Posology and method of administration

Posology

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

Adults and adolescents older than 12 years ($\geq 40\text{kg}$)

The recommended dosage of Brufen is 1200-1800 mg daily in divided doses. Some patients can be maintained on 600-1200 mg daily. Total daily dose should not exceed 2400 mg.

Paediatric Population

The recommended dose of Brufen is 20-30 mg per kg of bodyweight daily in divided doses. This can be achieved by using the suspension as follows:

| Age/weight | Frequency | Single dose |
|--------------------------|---------------------|-----------------|
| 3-6 months (~5-7kg) | Up to 3 times a day | 2.5ml (50mg) |
| 6-12 months (~7-10kg) | 3 times a day | 2.5ml (50mg) |
| 1 to 2 years | 3 to 4 times a day | 2.5ml |

| | | |
|------------------------------|--------------------|-----------------|
| (~10-14.5kg) | | (50mg) |
| 3 to 7 years (~14.5-25kg) | 3 to 4 times a day | 5ml (100mg) |
| 8 to 12 years (~25-40kg) | 3 to 4 times a day | 10ml (200mg) |

In juvenile rheumatoid arthritis, the daily dosage may be increased to 40 mg/kg bodyweight daily in severe cases. In children weighing less than 30 kg, the total daily dose of Brufen should not exceed 500 mg. The suspension is indicated in short-term use for the treatment of pyrexia in children over 3 months of age. Ibuprofen is not to be given to children under three months or children who weigh less than 5 kilograms.

Elderly

No special dosage modifications are required, unless renal or hepatic function is impaired, in which case dosage should be assessed individually.

Renal impairment

No dose reduction is required in patients with mild to moderate impairment to renal function (patients with severe renal insufficiency, see section 4.3).

Hepatic impairment

No dose reduction is required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction, see section 4.3).

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. Ensure the bottle is thoroughly shaken before use. A transient sensation of burning in the mouth or throat may occur with ibuprofen suspension.

For oral administration.

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Ibuprofen should not be given to patients who have experienced asthma, urticaria or allergic-type reactions after taking acetylsalicylic acid/ aspirin or other NSAIDs.
- Severe heart failure (NYHA IV).
- Severe liver failure.
- Severe renal failure (glomerular filtration below 30mL/min).
- Conditions involving an increased tendency or active bleeding.
- History of gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- Active, or history of recurrent peptic ulceration or gastrointestinal haemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding)
- During the third trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2).

Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

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)

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.

The use of Brufen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the potential for additive effects.

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.

Masking of symptoms of underlying infections

Brufen can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Brufen is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Elderly population

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

Gastrointestinal bleeding, ulceration and perforation

NSAIDs should be given with care to patients with a history of peptic ulceration and other gastro-intestinal disease since their conditions may be exacerbated (see section 4.3)

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (*See section 4.3*), and in the elderly. 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, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (*See below and section 4.5*).

The concomitant administration of Brufen and other NSAIDs, including cyclooxygenase-2 (Cox-2) selective inhibitors, should be avoided due to the increased the increased risk of ulceration or bleeding (*See below and section 4.5*).

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

Caution should be advised in 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 acetylsalicylic acid/aspirin (*See section 4.5*).

When GI bleeding or ulceration occurs in patients receiving Brufen, the treatment should be withdrawn.

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

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive 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 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. £ 1200mg 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 (2400mg/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 (2400mg/day) are required.

Cases of Kounis syndrome have been reported in patients treated with Brufen. 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.

Renal effects

Caution should be used when initiating treatment with Brufen 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 Brufen has resulted in renal papillary necrosis and other renal pathological changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandins 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 who are taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Haematological effects

As NSAIDs can interfere with platelet function and may prolong bleeding time, Brufen should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

Dermatological effects

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8). Most of these reactions occurred within the first month. If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

Exceptionally, 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.

Aseptic meningitis

Aseptic meningitis has been observed on rare occasions in patients with Brufen therapy. Although it is probably more likely to occur in patients with systematic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Information related to excipients

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. Brufen Paediatric oral suspension contains 3.3 g sucrose per 5 ml dose. This should be taken into account in patients with diabetes mellitus. May be harmful to the teeth.

This medicine contains 500 mg sorbitol in each 5 ml oral solution. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

Brufen Paediatric oral suspension contains methyl parahydroxybenzoate and propyl parahydroxybenzoate. May cause allergic reactions (possibly delayed).

Brufen Paediatric oral suspension contains sunset yellow (E110). May cause allergic reactions.

This medicine contains 12.5 mg sodium benzoate in each 5 ml oral solution. Sodium benzoate may increase jaundice in newborn babies (up to 4 weeks old).

This medicine contains less than 1 mmol sodium (23 mg) per 5ml dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Care should be taken in patients treated with any of the following drugs as interactions have been reported:

| Concomitant use of ibuprofen with: | Possible effects: |
|---|--|
| Other NSAIDs including cyclooxygenase-2 selective inhibitors | Concomitant use with other NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the potential for additive effects |
| Cardiac glycosides | NSAIDs may exacerbate heart failure, reduce glomerular filtration rate and increase plasma levels of cardiac glycosides |
| Corticosteroids | Increased risk of gastrointestinal ulceration or bleeding with NSAIDs |
| Anticoagulants | NSAIDs may enhance the effects of anticoagulants, such as warfarin |
| Antiplatelet agents & selective serotonin-reuptake inhibitors (SSRIs), e.g. clopidogrel and ticlopidine | Increased risk of gastrointestinal bleeding with NSAIDs |
| Acetylsalicylic acid/aspirin | As with other products containing NSAIDs, concomitant administration of ibuprofen and acetylsalicylic acid/aspirin is not generally recommended because of the potential of increased adverse effects. Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid/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 aspirin (acetylsalicylic acid) cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1) |
| Lithium | NSAIDs may decrease elimination of lithium |
| Anti-hypertensive, beta-blockers and diuretics | NSAIDs may reduce the effect of anti-hypertensives, such as ACE inhibitors, angiotensin-II receptor antagonists, beta-blockers and diuretics. Diuretics can also increase the risk of nephrotoxicity of NSAIDs |
| Methotrexate | NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate. |
| Cyclosporine | Increased risk of nephrotoxicity with NSAIDs |
| Tacrolimus | Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus |
| Zidovudine | Increased risk of haematological toxicity with NSAIDs are given with zidovudine. There is evidence of an increased risk of hemarthrosis and hematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen |
| 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. |
| 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. |
| Sulfonylureas | NSAIDs may potentiate the effects of sulfonylurea medications. There have |

| | |
|-----------------|--|
| | been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen. |
| Cholestyramine | The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown. |
| Aminoglycosides | NSAIDs may decrease the excretion of aminoglycosides. |
| Herbal extracts | Ginkgo biloba may potentiate the risk of bleeding with NSAIDs. |
| Mifepristone | A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs including acetylsalicylic acid. Limited evidence suggests that coadministration 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 |

4.6 Fertility, pregnancy and lactation

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.

Pregnancy

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.

From the 20th week of pregnancy onward, ibuprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

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.

Breastfeeding

In limited studies to date, ibuprofen appears in breast milk in very low concentrations. Brufen is not recommended for use in nursing mothers.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. 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 Undesirable effects

Gastrointestinal disorders

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis, duodenal ulcer & gastric ulcer and gastrointestinal perforation have been observed.

A transient sensation of burning in the mouth or throat may occur with ibuprofen suspension.

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).

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 the use of ibuprofen, the patient is therefore recommended to go to a doctor without delay.

Skin and subcutaneous tissue disorders

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)

Cardiac disorders and vascular disorders

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial studies suggest that use of ibuprofen, particularly at high dose (2400 mg/day), may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

The following are adverse reactions possibly related to ibuprofen, displayed by MedDRA frequency convention and system organ classification. Frequency groupings are classified according to the subsequent conventions: Very Common ($\geq 1/10$), 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 | Meningitis aseptic (see section 4.4) |
| Blood and lymphatic system disorders | Rare | Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia |
| Immune system disorders | Uncommon | Hypersensitivity |
| | Rare | Anaphylactic reaction |
| Psychiatric disorders | Uncommon | Insomnia, anxiety |
| | Rare | Depression, confusional state |
| Nervous system disorders | Common | Headache, dizziness |
| | Uncommon | Paraesthesia, somnolence |
| | Rare | Optic neuritis |
| Eye disorders | Uncommon | Visual impairment |
| | Rare | Toxic optic neuropathy |
| Ear and labyrinth disorders | Uncommon | Hearing impaired, tinnitus, vertigo |

| | | |
|--|-----------|---|
| Respiratory, Thoracic and mediastinal disorders | Uncommon | Asthma, bronchospasm, dyspnoea |
| Gastrointestinal disorders | Common | Dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melena, haematemesis, gastrointestinal haemorrhage |
| | Uncommon | Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation |
| | Very Rare | Pancreatitis |
| | Not known | Exacerbation of Colitis and Crohn's disease |
| Hepatobiliary disorders | Uncommon | Hepatitis, jaundice, hepatic function abnormal |
| | Very Rare | Hepatic failure |
| Skin and subcutaneous tissue | Common | Rash |
| | Uncommon | Urticaria, pruritus, purpura, angioedema, photosensitivity reaction |
| | Very Rare | Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis). |
| | Not known | Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP), Fixed Drug Eruption |
| Renal and urinary disorders | Uncommon | Nephrotoxicity in various forms, e.g. Tubulointerstitial nephritis, nephrotic syndrome and renal failure |
| General disorders and administration site conditions | Common | Fatigue |
| | Rare | Edema |
| Cardiac disorders | Very Rare | Cardiac failure, myocardial infarction (<i>see also section 4.4</i>) |
| Vascular disorders | Very Rare | Hypertension |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRC Pharmacovigilance Website: www.hpra.ie

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, hypothermia, renal effects, gastrointestinal bleeding, coma, apnea and depression of the CNS and respiratory system have also been rarely reported. Cardiovascular toxicity, including hypotension, bradycardia and tachycardia, has been reported. In cases of significant overdose, renal failure and liver damage are possible.

In serious poisoning, metabolic acidosis may occur.

Large overdoses are generally well tolerated when no other drugs are being taken.

Prolonged use at higher than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia.

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 the most current information, contact the local poison control centre.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: Anti-inflammatory and anti-rheumatic products, non-steroidal, propionic acid derivatives.

ATC Code: M01AE01

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

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid/aspirin on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics studies show that, when single doses of ibuprofen 400mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid/aspirin dosing (81mg), a decreased effect of acetylsalicylic acid/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/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.

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

Absorption

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

Distribution

Ibuprofen is extensively bound to plasma proteins (99%). 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 by the kidney is both rapid and complete. The elimination half-life of immediate release formulations is approximately two 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 young and elderly.

Paediatric population

The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5mg/kg to 10mg/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

There are no preclinical data of relevant for the safety assessments, apart from what has already been taken into account.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

Sucrose

Citric Acid Monohydrate

Sodium Benzoate (E211)

Agar BPC '54 Pdr

Glycerol (E422)

Sorbitol Solution Non-Crystallising (E420)

Polysorbate 80

Sunset Yellow FC Edicol (E110)

Orange Flavour D717

Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Once opened, the contents of the bottle should be used within 12 months.

6.4 Special precautions for storage

No special storage conditions.

6.5 Nature and contents of container

A 200 ml amber-coloured polyethylene terephthalate (PET) bottle with a pilfer-proof neck finish, fitted with an aluminium cap fitted with a LDPE liner.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Viatrix Healthcare Limited
Damastown Industrial Park

Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23355/012/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 1981

Date of last renewal: 02 March 2011

10 DATE OF REVISION OF THE TEXT

February 2026