

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen 200 mg Effervescent Tablets
Ibusolve 200 mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ibuprofen 200mg
Each tablet contains 661mg Sodium
For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and children over 12 years:

For the symptomatic relief of rheumatic or muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

4.2 Posology and method of administration

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4). For oral administration and short-term use only.

Adults and the elderly and children and adolescents between 12 and 18 years:

The minimum effective dose should be used for the shortest time necessary to relieve symptoms.

Adults

Initial dose - One or two tablets to be taken. The initial dose may be followed by further doses of one or two tablets every four hours. Leave at least four hours between doses and do not take more than 1200mg (6 tablets) in any 24 hour

period. To be taken preferably after food.

Adults should consult a doctor if symptoms persist or worsen, or if the product is required for more than 10 days.

Children and Adolescents (age range: ≥ 12 years to < 18 years)

Initial dose - One or two tablets to be taken. The initial dose may be followed by further doses of one or two tablets every four hours. If this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Leave at least four hours between doses and do not take more than 1200mg (6 tablets) in any 24 hour period. To be taken preferably after food.

Children

Not suitable for children under 12 years.

Directions

The tablets must be dissolved in half a glass of water (100ml). The tablets dissolve more quickly in warm water, or if stirred.

4.3 Contraindications

Ibuprofen is contraindicated in patients with hypersensitivity to active substance or to any of the excipients.

Ibuprofen should not be used in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin or other NSAIDs.

Ibuprofen is also contraindicated in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Ibuprofen should not be used in patients with active, or history of, recurrent peptic ulcer or gastrointestinal haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

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

Ibuprofen is contraindicated in patients with severe heart failure (NYHA Class IV), hepatic failure and renal failure (see section 4.4).

Ibuprofen is contraindicated during the last trimester of pregnancy (See section 4.6).

4.4 Special warnings and precautions for use

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

As with other NSAIDs, ibuprofen may mask the signs of infection.

The use of ibuprofen with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding (see section 4.5).

The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of analgesic medication. Patients with medication overuse headache should not be treated by increasing the dose of the analgesic. In such cases the use of analgesics should be discontinued.

The concomitant consumption of excessive alcohol with NSAIDs, including ibuprofen may increase the risk of adverse effects on the gastrointestinal tract, such as GI haemorrhage or the central nervous system, possibly due to an additive effect.

Elderly

The elderly have an increased frequency of adverse reactions due to NSAID, especially gastrointestinal bleeding and perforation, which may be fatal (see section 4.2).

Paediatric population

There is a risk of renal impairment in dehydrated children and adolescents

Gastrointestinal bleeding, ulceration and perforation

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime 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).

Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal 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 aspirin (see section 4.5)

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

NSAIDs should be given with care to patients with a history of ulcerative colitis or Crohn's disease as these conditions may be exacerbated (See section 4.8).

Respiratory disorders and hypersensitivity reactions

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 NSAIDs have been reported to precipitate bronchospasm, urticaria or angioedema in such patients.

Cardiac, renal and hepatic impairment

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. The habitual concomitant intake of various similar painkillers further increases this risk. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. For these patients, use the lowest effective dose, for the shortest possible duration and monitor renal function especially in long-term treated patients (see also section 4.3).

Ibuprofen should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with ibuprofen administration.

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, hypertension and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at high doses (2400mg/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. ≤ 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 (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 (2400 mg/day) are required.

Cases of Kounis syndrome have been reported in patients treated with Ibuprofen. 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 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 an NSAID may cause a dose dependant 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 and ACE inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment

state.

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.

SLE and mixed connective tissue disease

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders increased risk of aseptic meningitis (see below and section 4.8).

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).

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.

Masking of symptoms of underlying infections

Ibuprofen 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 Ibuprofen 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.

The label will include:

Read the enclosed leaflet before taking this product.

Do not take if you:

- have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding
- are allergic to ibuprofen, to any of the ingredients, or to aspirin or other painkillers
- are taking other NSAID pain killers or aspirin with a daily dose above 75 mg
- are in the last 3 months of pregnancy

Speak to a pharmacist or your doctor before taking if you:

- have or have had asthma, diabetes, high cholesterol, high blood pressure, a stroke, heart, liver, kidney or bowel problems
- Are a smoker
- Are pregnant
- are taking any other medicines
- have been advised to follow a low salt diet

Haematological effects

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

Aseptic meningitis

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

Impaired female fertility

The use of Ibuprofen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

Excipients

This medicinal product contains 661 mg sodium per tablet, equivalent to 33% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

The maximum daily dose of this product is equivalent to 198% of the WHO recommended maximum daily intake for sodium. Effervescent Tablets are considered high in sodium. This should be particularly taken into account for those on a low salt diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

- *Aspirin*: unless low-dose aspirin (not above 75mg daily) has been advised by a doctor as this may increase the risk of adverse reactions (see Section 4.4). 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).
- *Other NSAIDs including cyclooxygenase-2 selective inhibitors*: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4)

Ibuprofen should be used with caution in combination with:

Antihypertensives (ACE inhibitors and Angiotensin II Antagonists), beta-blockers and diuretics

Since NSAIDs may diminish the effects of these drugs. 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 coxib concomitantly with ACE inhibitors or angiotensin II antagonists. 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. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac 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.

Lithium

Decreased elimination of lithium.

Methotrexate

NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate.

Ciclosporin

Increased risk of nephrotoxicity.

Mifepristone

NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Corticosteroids

4.4). Increased risk of gastrointestinal ulceration or bleeding with NSAIDs (see section

Anticoagulants

4.4). NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section

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 hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding with NSAIDs (see section 4.4).

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 haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Aminoglycosides

NSAIDs may decrease the excretion of aminoglycosides.

Herbal extracts

Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

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

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 absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. 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 the following:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)

- Renal dysfunction, which may progress to renal failure with oligohydramnios.

At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the neonate to the following:

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

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

Lactation

In the limited studies so far available, NSAIDs can appear in the breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

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. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Adverse events which have been associated with Ibuprofen are given below, listed by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

The list of the following adverse effects relates to those experienced with ibuprofen at OTC doses (maximum 1200 mg per day), for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Gastrointestinal disorders: The most commonly observed adverse events are gastrointestinal in nature. Adverse events are mostly dose-dependent, in particular the risk of occurrence of gastrointestinal bleeding is dependent on the dosage range and duration of treatment.

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) (see section 4.4). 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, gastrointestinal haemorrhage and exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following ibuprofen administration. Less frequently, gastritis, duodenal ulcer, gastric ulcer and gastrointestinal perforation have been observed.

Immune system disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs. 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).

Cardiac disorders and vascular disorders: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical 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 such as myocardial infarction or stroke (see section 4.4).

Infections and infestations: Rhinitis and aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4). Exacerbation of infection-related inflammations 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.

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")

The following adverse reactions possibly related to ibuprofen and 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	Very Rare	Haematopoietic disorders (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia) First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

Immune system disorders	Uncommon	anaemia Hypersensitivity Urticaria and pruritus
	Very rare	Severe hypersensitivity reactions. Symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock).
	Not known	Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.
Psychiatric disorders	Uncommon	Insomnia, anxiety
	Rare	Depression, confusional state
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Paraesthesia. Somnolence Aseptic meningitis ²
	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, melaena, haematemesis, gastrointestinal haemorrhage
	Uncommon	Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation
	Very rare	Pancreatitis, peptic ulcer, perforation or

		gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis
	Not known	Exacerbation of colitis and Crohn's disease
Hepatobiliary disorders	Uncommon	Hepatitis, jaundice, hepatic function abnormal liver disorders
	Very rare	Hepatic failure

Skin and subcutaneous tissue disorders	Common	Various skin rashes
	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)

Renal and urinary disorders	Very rare	Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema. Nephrotoxicity in various forms e.g. Tubulointerstitial nephritis, nephrotic syndrome and renal failure
	Not known	Renal insufficiency Ureteric colic, dysuria Renal tubular acidosis*
General disorders and administration site conditions	Common	Fatigue
	Rare	Oedema
Investigations	Very rare	Decreased haemoglobin levels
Cardiac disorders	Very rare	Cardiac failure and oedema, myocardial infarction (also see section 4.4)
	Not Known	Kounis syndrome
Vascular disorders	Very rare	Hypertension
Metabolism and Nutrition Disorders	Not known	Hypokalaemia* Decreased appetite

Description of Selected Adverse Reactions

¹ Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm, dyspnoea or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

²The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug

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

*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 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 clinically 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 tinnitus, headache, dizziness, convulsion, and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea, diarrhea and depression of the CNS and respiratory system have also been rarely reported. In serious poisoning, metabolic acidosis may occur. Disorientation, excitation, fainting and cardiovascular toxicity, including hypotension, bradycardia and tachycardia have been reported. In cases of significant overdose acute renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other drugs are being taken.

In serious poisoning 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 and liver damage may occur.

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 and section 4.8).

Therapeutic measures

Patients should be treated symptomatically as required.

Within 1 hour of ingestion of a potentially toxic amount activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.
Renal and liver function should be closely monitored.
Patients should be observed for at least four hours after ingestion of potentially toxic amounts

Frequent or prolonged convulsions should be treated with intravenous diazepam.
Other measures may be indicated by the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: Anti-inflammatory and antirheumatic products, nonsteroidal; propionic acid derivatives.
ATC code: M01AE01

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics studies show that when single doses of Ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid 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 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 rapidly absorbed from the gastrointestinal tract, peak serum concentrations occurring 1-2 hours after administration. The elimination half-life is approximately 2 hours.

Ibuprofen is metabolised in the liver to two inactive metabolites and these, together with unchanged ibuprofen, are excreted by the kidney either as such or as conjugates. Excretion by the kidney is both rapid and complete.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate
Sodium carbonate (anhydrous)
Sodium cyclamate
Sodium saccharin
Citric acid anhydrous
Docusate sodium
Polyethylene glycol powder 6000
Povidone
Orange mint flavour 611160E
Mango flav-o-lok 610575E
IMS

6.2 Incompatibilities

None stated.

6.3 Shelf life

24 months unopened.

6.4 Special precautions for storage

Store in a cool dry place.

6.5 Nature and contents of container

Strip pack using PPFM laminate, constructed of: 40gsm MGBK paper / 12gsm LDPE / 8 μ aluminium foil / 23gsm LDPE. Strips are packed into a carton containing either 6, 10, 12 tablets

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Kent Pharmaceuticals Limited, Connect 38, 1, Dover Place, Ashford, Kent,
United Kingdom. TN23 1FB

8 MARKETING AUTHORISATION NUMBER(S)

PL 08215/0111

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
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