# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

IBUPROFEN 100 mg/5 ml oral suspension

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

5 ml oral suspension contains 100 mg ibuprofen.

Excipient(s) with known effect: sorbitol (E420) 1500 mg/5 ml, sodium benzoate (E211) 0.50 mg/5 ml, propylene glycol 12 mg/5 ml and aspartame (E951) 0.19 mg/5 ml.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Oral suspension

Off white to brownish homogenous suspension with apricot odour.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

IBUPROFEN is indicated for use in children, aged 3 months (weighing more than 5 kg) and upwards.

Short term symptomatic treatment of mild to moderate pain and fever.

Short-term symptomatic treatment of pain and feverishness associated with common cold and influenza.

### 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). For short term use only.

The recommended daily dose of the product is 20 – 30 mg per kg of body weight, divided into equal doses, with dosing intervals of 6 to 8 hours. Leave at least 4 hours between doses and do not take more than the recommended dose in 24 hours. The recommended dose should not be exceeded.

| **Age (Weight)** | **Body weight (kg)** | **Recommended Dosage** |
|---|---|---|
| Infants 3 - 6 months weighing more than 5 kg | 5-7.6 | 50 mg (one 2.5 ml dose may be taken 3 times in 24 hours) |
| Infants 6 - 12 months | 7.7 - 9 | 50 mg (one 2.5 ml dose may be taken 3 to 4 times in 24 hours) |
| Children 1 - 3 years | 10-16 | 100 mg (one 5 ml dose may be taken 3 times in 24 hours) |
| Children 4 - 6 years | 17-20 | 150 mg (7.5 ml (5ml +2.5ml) may be taken 3 times in 24 hours) |
| Children 7 - 9 years | 21-30 | 200 mg (10 ml) two 5ml doses may be taken 3 times in 24 hours |
| Children 10-12 years | 31-40 | 300mg (15ml) three 5ml doses may be taken 3 times in 24 hours |

Not suitable for children under 3 months of age unless advised by a doctor.
Do not use this product in children weighing less than 5 kg.

For infants aged 3 - 6 months medical advice should be sought if symptoms worsen or not later than 24 hours if symptoms persist.

If in children aged from 6 months this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

For children under 6 months medical advice should be sought after 24 hours use (3 doses) if the symptoms persist.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Method of administration
For oral administration and short-term use only.
To be taken preferably with or after food.
A plastic syringe (5 ml) is provided with the bottle to aid correct dosing.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients who have previously shown hypersensitivity reactions (e.g., asthma, rhinitis, angioedema, or urticaria) in response to acetylsalicylic acid or other non-steroidal anti- inflammatory drugs.

Active gastric or duodenal ulcer or a history of recurrent gastrointestinal ulcer/bleeding (two or more distinct episodes of proven ulceration or bleeding).

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Severe heart failure (NYHA Class IV), renal failure or hepatic failure (see section 4.4).

Bleeding diathesis and coagulation disorders.

Significant dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

Cerebrovascular or other active bleeding.

Children under 3 months of age.

Last trimester of pregnancy (see section 4.6).

## 4.4 Special warnings and precautions for use

The use of IBUPROFEN with concomitant NSAIDs, including cyclooxygenase 2 selective inhibitors, should be avoided.

Asthmatic patients are to seek their doctor's advice before using ibuprofen (see below).

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). Higher than recommended doses may cause serious risks.

IBUPROFEN should only be administered under strict consideration of the benefit-risk ratio in the following conditions:

- Systemic Lupus Erythematosus (SLE) or other autoimmune diseases
- Congenital disturbance of porphyrin metabolism (e.g. acute intermittent porphyria)
- The first and second trimester of pregnancy (see section 4.6)
- Lactation (see section 4.6)

Special care has to be taken in the following cases:

- Gastrointestinal diseases including chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease)
- Cardiac insufficiency and hypertension
- Reduced renal function
- Hepatic dysfunction
- Disturbed haematopoiesis
- Blood coagulation defects
- Allergies, hay fever, chronic swelling of nasal mucosa, adenoids, chronic obstructive airway disease or bronchial asthma as an increased risk of allergic reactions occurring in these patients. These allergic reactions may present as asthma attacks (so-called analgesic asthma) Quincke's oedema or urticaria
- Immediately after major surgical interventions

*Gastrointestinal bleeding, ulceration and perforation*
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 acetylsalicylic acid, or other medicinal products likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI toxicity, 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 or heparin, selective serotonin reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (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 gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

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

*Cardiovascular and cerebrovascular effects*
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension 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. ≤ 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 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.

*Severe cutaneous adverse reactions (SCARs)*
Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), and 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.

*Renal effects*
Ibuprofen may cause the retention of sodium, potassium and fluid in patients who have not previously suffered from renal disorders because of its effect on renal perfusion. This may cause oedema or even lead to cardiac insufficiency or hypertension in predisposed patients.

As with other NSAIDs, the prolonged administration of ibuprofen to animals has resulted in renal papillary necrosis and other pathological renal changes. In humans, there have been reports of acute interstitial nephritis with haematuria, proteinuria and occasionally nephrotic syndrome. Cases of renal toxicity have also been observed in patients in whom prostaglandins play 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 precipitate overt renal decompensation. Patients at greatest risk of suffering this reaction are those with renal dysfunction, heart failure, hepatic dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID treatment is generally 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.

There is a risk of renal impairment in dehydrated children, adolescents and the elderly.

*Allergic reactions*
Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of hypersensitivity reaction after taking the/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 as they could be at an increased risk of hypersensitivity reactions occurring with IBUPROFEN.

*Other precautions*
Bronchospasm, urticaria or angioedema may be precipitated in patients suffering from or with a previous history of bronchial asthma, chronic rhinitis, sinusitis, nasal polyps, adenoids or allergic diseases.

Ibuprofen may mask the signs or symptoms of an infection (fever, pain and swelling).

*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 nonhospital settings, the patient should consult a doctor if symptoms persist or worsen.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. 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 headache medications.

In general terms, the habitual intake of painkillers particularly on combination of several pain-relieving active substances, may lead to permanent renal damage with the risk of renal failure. This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore it should be avoided.

During treatment with ibuprofen, some cases with symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed in patients with existing auto-immune disorders (such as Systemic Lupus Erythematosus, mixed connective tissue disease).

Ibuprofen may temporarily inhibit platelet aggregation and prolong the bleeding time. Therefore, patients with coagulation defects or on anticoagulant therapy should be observed carefully.

In case of long term treatment with ibuprofen, a periodical monitoring of hepatic and renal function as well as the blood count is necessary, especially in high risk patients. Consumption of alcohol should be avoided since it may intensify side effects of NSAIDs, especially if affecting the gastrointestinal tract or the central nervous system.

Patients on ibuprofen should report to their doctor signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain or oedema.

Regarding female fertility, see section 4.6.

**IBUPROFEN contains 1500 mg sorbitol** in 5 ml oral suspension.
Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
Sorbitol may cause gastrointestinal discomfort and mild laxative effect.
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

**IBUPROFEN contains 0.19 mg aspartame** in 5 ml oral suspension.
Aspartame is a source of phenylalanine. Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. It may be harmful if the patient has phenylketonuria.

**IBUPROFEN contains less than 1 mmol (23 mg) sodium** in 10 ml oral suspension (maximum single dose), that is to say essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

*Ibuprofen should be avoided in combination with:*

Acetylsalicylic acid: Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects, unless low-dose acetylsalicylic acid (not above 75mg daily) has been advised by a doctor.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid 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:*

Anticoagulants: NSAIDS may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

Antihypertensives (ACE-inhibitors, beta-blockers, angiotensin-II receptor antagonists) and diuretics: NSAIDs may diminish the effect of these drugs. Diuretics can increase the risk of nephrotoxicity of NSAIDs. The concomitant administration of ibuprofen and potassium sparing diuretics or ACE-inhibitors can result in hyperkalaemia. Careful monitoring of potassium levels is necessary.

Captopril: Experimental studies indicate that ibuprofen counteracts the effect of captopril of increased sodium excretion.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4). NSAIDs should not be combined with anti-platelet agents such as ticlopidine due to the additive inhibition of the platelet function.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside (e.g. digoxin) levels.

Lithium: There is evidence for potential increases in plasma levels of lithium.

Methotrexate: NSAIDs inhibit the tubular secretion of methotrexate and certain metabolic interactions can occur resulting in decreased clearance of methotrexate. The administration of ibuprofen within 24 hours before or after the administration of methotrexate can lead to an elevated concentration of methotrexate and an increase in its toxic effects. Therefore, concomitant use of NSAIDs and high doses of methotrexate should be avoided. Also, the potential risk of interactions in low dose treatment with methotrexate should be considered, especially in patients with impaired renal function. In combined treatment, renal function should be monitored.

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.

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.

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.

Sulphonylureas: NSAIDs can increase the hypoglycemic effect of sulphonylureas. In the case of simultaneous treatment, monitoring of blood glucose levels is recommended.

Aminoglycosides: NSAIDs can slow down the elimination of aminoglycosides and increase their toxicity.

CYP2C9 inhibitors (e.g. voriconazole or fluconazole): 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.

Cholestyramine : Concomitant treatment with cholestyramine and ibuprofen results in prolonged and reduced (25%) absorption of ibuprofen. The medicinal products should be administered with at least two hours interval.

Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

Alcohol: The use of ibuprofen in individuals with chronic alcohol consumption (14-20 drinks/week or more) should be avoided due to increased risk of significant GI adverse effects, including bleeding.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the 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, 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 and 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, which may progress to renal failure with oligohydramnios (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 section 4.3).

Breastfeeding

Ibuprofen is excreted in breast milk, but with therapeutic doses during short term treatment, the risk for influence on the infant seems unlikely. If, however, longer treatment is prescribed, early weaning should be considered.

Fertility

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

## 4.7 Effects on ability to drive and use machines

Ibuprofen generally has no adverse effects on the ability to drive and use machinery. However since at high dosage side effects such as fatigue, somnolence, vertigo (reported as common) and visual disturbances (reported as uncommon) may be experienced, the ability to drive a car or operate machinery may be impaired in individual cases. This effect is potentiated by simultaneous consumption of alcohol.

## 4.8 Undesirable effects

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 has been observed.

Undesirable effects are mostly dose-dependent. Especially the risk for the occurrence of gastrointestinal bleedings depends on the dosage range and duration of the treatment. Other known risk factors, see section 4.4.

Hypersensitivity reactions have been reported and these may consist of:
(a) non-specific allergic reactions and anaphylaxis

(b) respiratory tract reactivity, e.g. asthma, aggravated asthma, bronchospasm, dyspnoea
(c) various skin reactions, e.g. pruritus, urticaria, purpura, angioedema and very rarely exfoliative and bullous dermatoses (including Stevens-Johnson syndrome, toxic epidermal necrolysis).

Exacerbation of 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 recommended to go to a doctor without delay.

In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection.

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

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

Adverse events at least possibly related to ibuprofen are displayed by MedDRA frequency convention and system organ class. The following frequency groupings are used: 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 |
| | Very rare | Aseptic meningitis |
| **Blood and lymphatic system disorders** | Very rare | Leucopoenia, thrombocytopenia, neutropenia, agranulocytosis aplastic anaemia and haemolytic anaemia. The first symptoms or signs may include: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion unexplained bleeding and bruising. |
| **Immune system disorders** | Uncommon | Hypersensitivity reactions such as urticaria, pruritus, purpura and exanthema as well as asthma attacks (sometimes with hypotension) |
| | Rare | Lupus erythematosus syndrome |
| | Very rare | Severe hypersensitivity reactions. The symptoms may include: facial oedema, swelling of the tongue, internal laryngeal swelling with constriction of the airways, dyspnoea, tachycardia, fall of blood pressure to the point of life-threatening shock. |
| **Metabolism and nutrition disorders** | Not known | Decreased appetite, hypokalaemia*. |
| **Psychiatric disorders** | Uncommon | Anxiety |
| | Rare | Depression, confusional state, hallucinations |
| **Nervous system disorders** | Common | Headache, somnolence, agitation, dizziness, insomnia, irritability |
| | Uncommon | Paraesthesia, |
| | Rare | Optic neuritis |
| **Eye disorders** | Uncommon | Visual impairment |

| | | |
|---|---|---|
| | Rare | Toxic optic neuropathy |
| **Ear and labyrinth disorders** | Common | Vertigo |
| | Uncommon | Impaired hearing |
| | Very rare | Tinnitus |
| **Cardiac disorders** | Very rare | Palpitations, heart failure, myocardial infarction, acute pulmonary oedema, oedema |
| | Not known | Kounis syndrome |
| **Vascular disorders** | Very rare | Hypertension |
| **Respiratory, thoracic and mediastinal disorders** | Uncommon | Asthma,bronchospasm, dyspnoea |
| **Gastrointestinal disorders** | Common | Dyspepsia, diarrhoea, nausea, vomiting abdominal pain, flatulence, constipation |
| | Uncommon | Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation |
| | Very rare | Oesophagitis, pancreatitis,intestinal strictures, melena, haematemesis, gastrointestinal haemorrhage |
| | Not known | Colitis and Crohn's disease |
| **Hepatobiliary disorders** | Uncommon | Hepatitis, jaundice, hepatic function abnormal |
| | Rare | Liver injury |
| | Very rare | Hepatic failure |
| **Skin and subcutaneous tissue disorders** | Uncommon | Rash, urticaria, pruritus, purpura, photosensitivity reaction |
| | Very rare | Severe cutaneous adverse reactions (SCARs) (including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis)<br>Alopecia<br>Necrotising fasciitis |
| | Not known | Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)<br>Acute generalised exanthematous pustulosis (AGEP) |
| **Renal and urinary disorders** | Very rare | Tubulointerstitial nephritis, nephrotic syndrome and renal failure,<br>acute renal failure, papillary necrosis (especially in long-term use associated with increased serum urea ) |
| | Not known | Ureteric colic, dysuria, renal tubular acidosis*. |
| **General disorders and administration site conditions** | Common | Fatigue |
| | Rare | Oedema |

*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

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

**Symptoms**
Most patients who have ingested clinically important amounts of NSAIDs will manifest symptoms within 4 to 6 hours. The most frequently reported symptoms include nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache, dizziness, confusion and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. Children may also develop myoclonic cramps. 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, liver damage, fainting, hypotension, nystagmus, hypothermia, respiratory depression and cyanosis 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). Exacerbation of asthma is possible in asthmatics.

**Management**
A specific antidote does not exist. Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.
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.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, Non-Steroids, Propionic acid derivates, ATC code: M01AE01

Mechanism of action

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. The drug's therapeutic effects as an NSAID are thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis.

Clinical efficacy and safety

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400mg were taken within 8 hours before or within 30 minutes after immediate release acetylsalicylic acid dosing (81mg), 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 cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

## 5.2 Pharmacokinetic properties

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. If administered with food, peak serum concentrations are lower and achieved more slowly than when taken on an empty stomach. Food does not affect markedly total bioavailability.

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 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 young and elderly.

***Paediatric population***

The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5mg/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 unbound (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 about1% 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 relevance for the safety assessment, apart from what has already been taken into account in this summary of product characteristics.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Glycerol

Sorbitol, 70% liquid non-crystallizing (E420)

Xanthan gum

Microcrystalline Cellulose and Carmellose Sodium

Polysorbate grade 80

Disodium edetate

Saccharin sodium

Citric acid monohydrate

Sodium citrate dihydrate

Sodium benzoate (E211)

Flavour Apricot containing:

- Propylene glycol
- Flavouring substance
- Natural flavouring substance
- Orange oil, Lemon oil

Taste masking flavour containing:

- Potato maltodextrin
- Flavouring components
- Aspartame (E951)
- Acesulfame-K (E950)

Emulsion Simethicone 30%

Sodium chloride

Water, purified

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

Unopened suspension: 3 years.

After first opening the suspension can be stored for 3 months.

## 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

100 ml oral suspension is immediate packed in a 125 ml brown neutral glass bottle supplied with a polypropylene screw cap with a polyethylene sealing or alternative polypropylene screw cap child-resistant tamper evident ring with embossing and liner.

Cardboard box contains one (1) bottle, one plastic 5 ml graduated oral syringe for dosing, and an instruction leaflet. The 5 ml plastic oral syringe for dosing is graduated on 2.5 ml and 5 ml for measuring of the doses.

### 6.6 Special precautions for disposal

Shake the medicine bottle well before each use.

A graduated plastic oral syringe is used for measuring the required amount of suspension. The plastic syringe is included in the package.

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

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