SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BRUFEN 20 mg/ml Oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BRUFEN 20 mg/ml Oral suspension
1 millilitre of oral suspension contains:
- Active substance: ibuprofen 20mg;
- Excipients with known effect: methylparahydroxybenzoate (1mg), propylparahydroxybenzoate (0.5mg), liquid sorbitol (100mg), sucrose (660mg), sunset yellow E110 (0.1mg), sodium benzoate (2.5mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BRUFEN 20 mg/ml Oral suspension is indicated:
▪ in short-term treatment of fever and pain in children; ▪ in treatment of juvenile rheumatoid arthritis symptoms.

4.2 Posology and method of administration

Posology
The average daily dose in children is 20 mg/kg/day, divided in 3 to 4 administrations, as described in the table below.

For correct calculation of the daily dose of the medicinal product, consider that 1kg of the child's body weight corresponds to 1ml of oral suspension, equal to 20mg of ibuprofen (for example, if a child weighs 9kg, administer 9ml of suspension per day, corresponding to 180mg of ibuprofen). To calculate the single dose, the daily dose must be divided into 3 to 4 administrations.

BRUFEN 20 mg/ml Oral suspension is not recommended in children who weigh less than 7kg.

The doctor must be consulted in the case that use of the medicinal product should be required for longer than
3 days in infants and toddlers aged over 6 months and in adolescents, or in the event of worsening symptoms.

In infants aged 3 to 5 months the doctor must be consulted should the symptoms persist longer than 24 hours or in the event of worsening symptoms.

Undesirable effects can be minimised by using the lowest effective dose for the shortest possible duration of treatment necessary to control symptoms (see section 4.4).

The oral suspension may be administered with the dosing syringe supplied with the medicinal product. The table below takes into account the daily total amount of ibuprofen divided in 3 daily administrations.

Body weight (kg)	**Quantity of ibuprofen (mg per dose)**	**Corresponding volume (ml per dose)**
7	46.7	2.3
9	60	3
12	80	4
15	100	5
18	120	6
21	140	7
24	160	8
27	180	9
30	200	10

After opening, the content of the bottle has a shelf life of 6 months, if correctly stored.

Special populations
Renal insufficiency: in patients with mild to moderate decrease in renal function, the dose should be kept as low as possible for the shortest duration required to control symptoms and renal function should be monitored.

Hepatic insufficiency: in patients with mild to moderate decrease in hepatic function, the dose should be kept as low as possible for the shortest duration required to control symptoms and hepatic function should be monitored. BRUFEN is contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Method of administration
− Oral use.

- Ensure that the bottle of BRUFEN Oral suspension is completely stirred before use. A transient burning sensation in the mouth or throat might occur with BRUFEN Oral suspension.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Subjects with hypersensitivity to acetylsalicylic acid or other analgesics, antipyretics, non-steroid antiinflammatory drugs (NSAIDs), particularly when the hypersensitivity is associated with nasal polyps, angioedema and/or asthma.
Severe hepatic insufficiency.
Severe renal insufficiency (glomerular filtration below 30 ml/min).
Severe cardiac insufficiency (NYHA class IV).
Severe dehydration (caused by vomiting, diarrhoea or insufficient liquid intake).
Severe or active peptic ulcer.
History of gastrointestinal haemorrhage or perforation related to previous active treatments or history of recurrent peptic haemorrhage/ulcer (two or more distinct episodes of proven ulceration or bleeding).
During the third trimester of pregnancy (see section 4.6).
Patients with clinical conditions leading to an increase of bleeding.
Ibuprofen use is not recommended in children with a body weight less than 7 kg.

4.4 Special warnings and precautions for use

BRUFEN use concomitantly with other NSAIDs, including selective cyclooxygenase-2 (COX-2) inhibitors, should be avoided due to an increased risk of ulceration or bleeding (see section 4.5).

Undesirable effects may be minimised by using the lowest effective dose for the shortest possible length of treatment required to control symptoms (see section 4.2 and the sections below on gastrointestinal and cardiovascular risks).

With prolonged use of any painkiller, you may experience headaches that should not be treated with an increased dose of the medicinal product.

Taking other NSAIDs or alcohol concomitantly with BRUFEN may worsen the undesirable effects related to the active substance, particularly those affecting the gastrointestinal tract or central nervous system (see section 4.8).

Elderly
Elderly patients have increased frequency of adverse reactions to NSAIDs, especially gastrointestinal haemorrhages and perforations, which may be fatal (see section 4.2).

Gastrointestinal haemorrhage, ulceration and perforation

Gastrointestinal haemorrhage, ulceration and perforation, which may be fatal, have been reported during treatment with all NSAIDs, at any time, with or without warning symptoms or a previous history of severe gastrointestinal events.

In elderly patients and patients with a history of ulcer, especially if complicated by haemorrhage or perforation (see section 4.3), the risk of gastrointestinal haemorrhage, ulceration or perforation is higher with increased NSAIDs doses. These patients should start treatment with the lowest available dose. For these patients as well as for patients taking low doses of acetylsalicylic acid, or other medicinal products that may increase the risk of gastrointestinal events, concomitant use of gastroprotective agents (misoprostol or proton pump inhibitors) must be considered (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, particularly the elderly, must report any unusual gastrointestinal symptoms (especially gastrointestinal haemorrhage) particularly in the early stages of treatment.

Caution must be exercised with patients taking concomitant medicinal products that might increase the risk of ulceration or haemorrhage, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors (SSRIs) or platelet antiaggregates such as acetylsalicylic acid (see section 4.5).

Treatment must be suspended when gastrointestinal haemorrhage or ulceration occurs in patients taking Brufen.

NSAIDs must be administered with caution to patients with a history of peptic ulcer and other gastrointestinal diseases (e.g. ulcerative colitis, Crohn's disease), as these conditions may be exacerbated (see sections 4.3 and 4.8).

Use with caution also in patients with coagulation defects.

Cardiovascular and cerebrovascular effects

Adequate monitoring and suitable instructions are required in patients with a positive history of hypertension, cardiac insufficiency and/or mild to moderate congestive cardiac insufficiency because, in association with treatment with NSAIDs like ibuprofen, fluid retention and oedema have been reported.

NSAIDs may reduce the effect of diuretics and other anti-hypertensive medicinal products (see section 4.5).

Clinical studies suggest that use of ibuprofen, particularly at high doses (2,400 mg/day), may be associated with a moderately increased risk of arterial thrombotic events (such as myocardial infarction or stroke). In general, epidemiological studies do not suggest that low doses of ibuprofen (such as □1,200 mg/day) are associated to an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive cardiac insufficiency (NYHA class II-III), established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease should be treated with ibuprofen only after careful consideration and high doses (2,400 mg/day) must be avoided.
Similar assessment should be carried out before starting a long-term treatment in patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking), especially when high doses (2,400 mg/day) of ibuprofen are required.

Dermatological effects

Very rarely, severe skin reactions, some of them fatal—including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis—have been reported in association with the use of NSAIDs (see section 4.8). In the early stages of therapy, patients appear to be at higher risk: the onset of the reaction occurs within the first month of treatment in most cases. Acute generalised exanthematous pustulosis (AGEP) in relation to medicinal products containing ibuprofen has been reported. Treatment with BRUFEN must be stopped upon first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity, as well as occurrence of visual disorders or persistent signs of hepatic dysfunction.

Exceptionally, chickenpox can cause severe infectious skin and soft tissue complications. Currently, the role of NSAIDs in the worsening of these infections cannot be excluded. Therefore, it is recommended to avoid using ibuprofen in case of chickenpox.

Renal effects

When initiating treatment with ibuprofen, caution must be exercised with significantly dehydrated patients.

Ibuprofen may cause water and sodium, potassium retention in patients who have never suffered from renal disorders because of its effects on renal perfusion. This may cause oedema, cardiac insufficiency or high blood pressure in susceptible patients.

The long-term use of ibuprofen, as with other NSAIDs, has resulted in renal papillary necrosis and other pathological renal changes.

In general, the habitual use of analgesics, especially associations of various active analgesic substances, may lead to permanent renal damage, with risk of renal insufficiency (analgesic nephropathy).

Renal toxicity was observed in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. The administration of NSAIDs in these patients may result in a dose-dependent reduction in prostaglandin formation and, as a secondary effect, in renal blood flow that may quickly lead to renal failure.

Patients most at risk of these reactions are those with impaired renal function, cardiac failure, hepatic dysfunctions, the elderly and all the patients taking diuretics and ACE inhibitors. Discontinuation of NSAID therapy is usually followed by recovery to pretreatment state.
Renal function must be monitored in the event of prolonged use, particularly in the case of widespread lupus erythematosus.

There is a risk of altered renal function in dehydrated children and adolescents and in elderly patients.

Respiratory disorders
BRUFEN should be prescribed with caution in patients with bronchial asthma, chronic rhinitis or allergic diseases either past or present because bronchospasm, urticaria or angioedema might arise. The same holds true for those subjects who experienced bronchospasm after the use of acetylsalicylic acid or other NSAIDs.

Hypersensitivity reactions
Analgesics, antipyretics, non-steroidal anti-inflammatory drugs may cause potentially severe hypersensitivity reactions (anaphylactic reactions) even in patients not previously exposed to this type of medicinal products.
The risk of hypersensitivity reactions after taking ibuprofen is greater in subjects who have shown such reactions after using other analgesics, antipyretics, non-steroidal anti-inflammatory drugs. Therefore, caution is required with these patients.
Caution is also required in patients with bronchial hyperreactivity (asthma), hay fever, nasal polyps or chronic obstructive respiratory diseases or a history of angioedema, given that these patients are more likely to experience allergic reactions (see sections 4.3 and 4.8).
Hypersensitivity reactions may occur in the form of asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria.
Severe acute hypersensitivity reactions (e.g. anaphylaxis) have been observed rarely. Treatment must be stopped at the first signs of hypersensitivity reaction after ibuprofen administration.
Medical support measures must be initiated by specialist medical personnel, in line with the symptoms.

Impaired cardiac, renal and hepatic function
Special caution should be exercised in treating patients with impaired cardiac, hepatic or renal function, as the use of NSAIDs may result in deterioration of renal function.

Regular concomitant use of several painkillers may further increase this risk. In patients with impaired cardiac, hepatic or renal function it is recommended to use the lowest effective dose for the shortest period of treatment and to carry out regular monitoring of clinical and laboratory parameters, especially in the case of prolonged treatment (see section 4.3).

Haematological effects
Ibuprofen, like other NSAIDs, may inhibit platelet aggregation and has been shown to prolong bleeding time in healthy subjects. Therefore, patients with coagulation defects or on anticoagulant therapy should be monitored carefully.

Aseptic meningitis
On rare occasions, aseptic meningitis symptoms have been observed in patients being treated with ibuprofen. Although this is more likely to occur in patients with systemic lupus erythematosus and related connective tissue conditions, it has also been observed in patients who did not display concomitant chronic conditions (see section 4.8).

Masking of symptoms of underlying infections
BRUFEN may mask symptoms of infection, which might delay the start of adequate treatment and, therefore, worsen the outcome of the infection. This has been observed in community-acquired bacterial pneumonia and bacterial complications of chickenpox. When BRUFEN is administered to relieve fever or pain related to infection, the infection should be monitored. In non-hospital settings, the patient should seek medical attention if symptoms persist or worsen.

Since ocular alterations have been detected during animal studies with non-steroidal anti-inflammatory drugs, in case of prolonged treatment it is recommended to perform periodic ophthalmologic monitoring.

BRUFEN use, as for any medicinal product inhibiting the synthesis of prostaglandins and cyclooxygenase, is not recommended in women planning to have a baby (see section 4.6).
Administration of BRUFEN should be suspended in women who have fertility problems or who are undergoing fertility investigations.

Important information on some excipients BRUFEN Oral suspension contains:

Sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucraseisomaltase deficiency should not take this medicinal product. It contains 3.3g of sucrose for a dose of 5ml.
This should be taken into account for patients with diabetes mellitus. It may be harmful to teeth.

Sorbitol
This medicinal product contains 500mg of sorbitol for a dose of 5ml. Patients with hereditary fructose intolerance should not take this medicinal product.

Methylparahydroxybenzoate and propylparahydroxybenzoate They may cause allergic reactions (even delayed).

Sunset yellow (E110)
It may cause allergic reactions.

Sodium benzoate (E211)
This medicinal product contains 12.5mg of sodium benzoate for a dose of 5ml. Sodium benzoate may increase jaundice in infants aged up to 4 weeks.

BRUFEN Oral suspension contains less than 1mmol (23mg) of sodium per dose, that is essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen (like other NSAIDs) should be taken with caution in combination with the substances listed below.

Corticosteroids: they may increase the risk of gastrointestinal ulceration or haemorrhage (see section 4.4).

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin or heparin (see section 4.4). In case of concomitant treatment, monitoring the coagulation state is recommended.

COX-2 inhibitors and other NSAIDs: these substances can cause an increased risk of adverse reactions in the gastrointestinal tract (see section 4.4).

Acetylsalicylic acid: generally, concomitant administration of ibuprofen and acetylsalicylic acid is not recommended due to the potential increase of undesirable effects.
Experimental data suggest that ibuprofen may competitively inhibit the effects of low-dose acetylsalicylic acid on platelet aggregation when these two medicinal products are administered concomitantly. Although there are uncertainties regarding the extrapolation of these data to the clinical situation, it is impossible to exclude that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid. Occasional ibuprofen use is unlikely to result in clinically significant effects (see section 5.1). In any case, ibuprofen should not be combined with acetylsalicylic acid or other NSAIDs, including selective cyclooxygenase-2 inhibitors, for potential additive effect (see section 4.4).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): they may lead to an increased risk of gastrointestinal haemorrhage (see section 4.4).

Antihypertensive medicinal products, beta blockers, diuretics, ACE inhibitors and angiotensin II antagonists: NSAIDs may reduce the effect of diuretics and other anti-

hypertensive medicinal products. Diuretics may also increase the risk of nephrotoxicity associated with NSAIDs.
In some patients with impaired renal function (e.g. dehydrated or elderly patients), co-administration of an ACE inhibitor, a beta blocker or an angiotensin II antagonist and of agents that inhibit the cyclooxygenase system may result in further deterioration of renal function, leading to possible acute renal insufficiency, which is usually reversible. These interactions must be taken into consideration in patients taking Brufen concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, this combination must be administered with caution, especially in elderly patients.
Patients must be adequately hydrated and it is essential to take into consideration monitoring renal function after the start of the concomitant treatment and in subsequent periods.

Phenytoin and lithium: concomitant administration of ibuprofen and phenytoin or lithium preparations may lead to reduced elimination of these medicinal products resulting in an increase of their plasma levels, possibly reaching the toxic threshold. Where this association is deemed necessary, monitoring of phenytoin and lithium plasma levels is recommended in order to adjust the dose during concomitant treatment with ibuprofen.

Methotrexate: NSAIDs may inhibit the tubular secretion of methotrexate and certain metabolic interactions may occur resulting in decreased methotrexate clearance and increased risk of toxicity.

Moclobemide: it enhances the effect of ibuprofen.

Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides increasing their toxicity.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma levels of cardiac glycosides. It is recommended to monitor the levels of serum glycosides.

Cholestyramine: concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance of this interaction is not known.

Ciclosporines: concomitant administration of cyclosporine and some NSAIDs causes an increased risk of renal damage. This effect cannot be ruled out for the association of cyclosporine and ibuprofen.

Plant extracts: Ginkgo Biloba may increase the risk of bleeding if taken in association with NSAIDs.

Mifepristone: due to the anti-prostaglandin properties of NSAIDs, their use after administration of mifepristone may theoretically lead to a reduction in the effect of

the medicinal product. The limited evidence suggests that co-administration of NSAIDs and prostaglandins on the same day does not adversely affect the effects of mifepristone or prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of the medicinal product on abortion.

Quinolone antibiotics: patients taking NSAIDs and quinolones may increase the risk of developing seizures.

Sulphonylureas: NSAIDs may increase the hypoglycaemic effect of sulphonylureas. In the event of concomitant treatment, monitoring levels of blood glucose is recommended.

Tacrolimus: co-administration of NSAIDs and tacrolimus may increase the risk of nephrotoxicity.

Zidovudine: there is evidence of an increased risk of haemarthroses and haematoma in HIV-positive haemophilia patients in concomitant treatment with zidovudine and other NSAIDs. A haematological examination is recommended 1 to 2 weeks after the start of treatment.

Ritonavir: it may result in increased plasma concentrations of NSAIDs.

Probenecid: it may slow ibuprofen excretion, resulting in increased plasma concentrations of ibuprofen.

CYP2C9 inhibitors: concomitant administration of ibuprofen and CYP2C9 inhibitors may slow ibuprofen elimination (CYP2C9 substrate), causing an increase in exposure to ibuprofen. A study with voriconazole and fluconazole (CYP2C9 inhibitors) highlighted increased exposure to S(+)-ibuprofen from about 80% to 100%. Reducing the ibuprofen dose should be taken into consideration in cases of co-administration with strong CYP2C9 inhibitors.

Alcohol, bisphosphonates and oxpentifylline (pentoxifylline): they may enhance the gastrointestinal side effects and the risk of bleeding and ulcers.

Baclofen: high baclofen toxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo-foetal development.
Results of epidemiological studies suggest an increased risk of abortion, cardiac malformation and gastroschisis after the use of a prostaglandin synthesis inhibitor in the early stages of pregnancy. The absolute risk of cardiac malformations increased from less than 1% to about 1.5%. The risk is thought to increase with dose and duration of the therapy. In animals, administration of prostaglandin

synthesis inhibitors showed to cause an increase in loss of pre- and post-implantation and embryo-foetal mortality.
Furthermore, an increased incidence of various malformations, including cardiovascular, has been reported in animals which were administered prostaglandin synthesis inhibitors during the organogenesis period.

BRUFEN must not be administered during the first and second trimester of pregnancy except when strictly necessary.

If BRUFEN is used by a woman attempting to conceive or during the first and second trimester of pregnancy, the dose and duration of treatment should be kept as low as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); • renal dysfunction, which can progress to renal insufficiency with oligo-hydroamnios;

the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time and anti-aggregation effect which can occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

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

Breast-feeding
Ibuprofen is excreted in breast milk: at therapeutic doses, during short-term treatment, the risk of influence on the neonate seems unlikely, while in case of long-term treatment early weaning should be considered. If possible, NSAIDs should be avoided during breast-feeding.

Fertility
Ibuprofen use may impair female fertility and is not recommended in women attempting to conceive. It has been shown that medicinal products that inhibit cyclooxygenase/prostaglandin synthesis can cause impairment of female fertility due to an effect on ovulation. This effect is reversible when treatment is stopped. In women who have difficulty conceiving or who are under infertility investigation, stopping treatment with ibuprofen should be considered.

4.7 Effects on ability to drive and use machines

During treatment with ibuprofen, patient reaction times can be altered due to the possible occurrence of undesirable effects such as headache, drowsiness, dizziness, fatigue and altered vision. This must be taken into consideration when greater vigilance is required, such as when driving and using machines. This is especially important during concomitant alcohol intake.

4.8 Undesirable effects

The undesirable effects observed with ibuprofen are generally common to other analgesics, antipyretics, nonsteroidal anti-inflammatory drugs.

Gastrointestinal conditions
The most commonly observed adverse events are gastrointestinal. Peptic ulcers, gastrointestinal haemorrhage or perforation, sometimes fatal, may occur, particularly in elderly patients (see section 4.4). Gastrointestinal perforation with ibuprofen use has been observed rarely.
After BRUFEN administration, the following effects were reported: nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, epigastric pain, heartburn, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4).
Uncommon: gastritis.
Very rare: pancreatitis.

Immune system disorders
Hypersensitivity reactions have been reported following treatments with NSAIDs.
These may consist of: a) non-specific allergic reaction and rarely anaphylaxis;
b) uncommon: reactions in the respiratory tract including asthma, even severe, bronchospasm or dyspnoea;
c) a variety of common skin disorders, such as various types of rash, uncommon ones such as pruritus, urticaria, purpura, angioedema and, very rarely, exfoliative and bullous dermatitis (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme).

Furthermore, the lupus erythematosus syndrome has also been rarely reported.

Cardiac and vascular conditions
Oedema, fatigue, hypertension and cardiac insufficiency have been reported in association with NSAID treatment.
Clinical studies suggest that use of ibuprofen, particularly at high doses (2,400 mg/day), may be associated with a moderately increased risk of arterial thrombotic events, such as myocardial infarction or stroke (see section 4.4).
Very rare: palpitations, cardiac insufficiency, myocardial infarction, acute pulmonary oedema, oedema, hypertension.

Other events reported with less frequency and for which causality was not necessarily established include:

Haemolymphopoietic system conditions
Rare: leukopaenia, thrombocytopaenia, neutropaenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Psychiatric disorders
Uncommon: insomnia, anxiety.

Rare: depression, confusion.
Hallucinations.

Nervous system conditions
Common: headache, dizziness.
Uncommon: paraesthesia, drowsiness.
Rare: optic neuritis, aseptic meningitis.

Infections and infestations
Rhinitis and aseptic meningitis (especially in patients with pre-existing auto-immune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of neck stiffness, headache, nausea, vomiting, fever or disorientation (see section 4.4). Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) has been described.
Uncommon: rhinitis.
Rare: aseptic meningitis.

Respiratory tract conditions
Uncommon: bronchospasm, dyspnoea, apnoea.

Eye conditions
Uncommon: impaired vision.
Rare cases of ocular changes resulting in visual impairment, toxic optic neuropathy.

Ear and labyrinth conditions
Uncommon: impaired hearing, tinnitus, dizziness.

Hepatobiliary conditions
Uncommon: hepatitis and jaundice, impaired renal function. Very rare: renal insufficiency.

Skin and subcutaneous tissue conditions
Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare), and photosensitivity reaction (uncommon). In exceptional cases, severe skin infections and soft tissue complications may occur during chickenpox infection (see "Infections and infestations" and section 4.4). Not known: drug reaction with eosinophilia, systemic symptoms (DRESS syndrome) and acute generalised exanthematous pustulosis (AGEP).

Renal and urinary conditions
Uncommon: loss of renal function and toxic nephropathy in various forms, including interstitial nephritis, nephrotic syndrome and renal insufficiency.

Systemic disorders and administration site conditions Malaise.
Common: fatigue.

Rare: oedema.

The following adverse reactions possibly related to ibuprofen are presented according to the MedDRA frequency convention and system organ class. Frequency groups are classified according to the following conventions: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000,<1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000) and not known (which cannot be defined on the basis of available data).

Organ system class	**Frequency**	**Adverse reaction**
Infections and infestations	Uncommon	Rhinitis
	Rare	Aseptic meningitis (see section 4.4).
Haemolymphopoietic system conditions	Rare	Leukopaenia, thrombocytopaenia, neutropaenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.
Immune system disorders	Uncommon	Hypersensitivity
	Rare	Anaphylactic reaction
Psychiatric disorders	Uncommon	Insomnia, anxiety.
	Rare	Depression, confusion.
Nervous system conditions	Common	Headache, dizziness.
	Uncommon	Paraesthesia, drowsiness.
	Rare	Optic neuritis
Eye conditions	Uncommon	Visual impairment
	Rare	Toxic optic neuropathy.
Ear and labyrinth conditions	Uncommon	Impaired hearing, tinnitus, dizziness.
Respiratory, thoracic and mediastinal conditions	Uncommon	Asthma, bronchospasm, dyspnoea.
Gastrointestinal conditions	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
	Not known	Exacerbation of colitis and Crohn's disease.

Hepatobiliary conditions	Uncommon	Hepatitis, jaundice, abnormal hepatic function.
	Very rare	Hepatic insufficiency
Skin and subcutaneous tissue conditions	Common	Rash
	Uncommon	Urticaria, pruritus, purpura, angioedema, photosensitivity reaction.
	Very rare	Severe skin reactions (e.g. erythema multiforme, bullous reactions including 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 conditions	Uncommon	Nephrotoxicity in various forms, e.g. tubulointerstitial nephritis, nephrotic syndrome and renal insufficiency.
Systemic disorders and administration site conditions	Common	Fatigue
	Rare	Oedema
Cardiac conditions	Very rare	Cardiac insufficiency, myocardial infarction (see section 4.4).
Vascular conditions	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 the national reporting system at the address https://www.aifa.gov.it/en/content/segnalazioni-reazioni-avverse.

4.9 Overdose

Toxicity
Toxicity signs and symptoms have not generally been observed at doses lower than 100 mg/kg in children or in adults. However, in some cases supporting treatment may be required. It has been observed that children show toxicity signs and symptoms after ingesting ibuprofen at doses of 400 mg/kg or higher.

Symptoms
Most patients who have ingested significant amounts of ibuprofen will experience symptoms within 4 to 6 hours.
The most commonly reported symptoms of overdosing include: nausea, vomiting, abdominal pain, lethargy and drowsiness.
The effects on the central nervous system (CNS) include headache, tinnitus, dizziness, convulsions and loss of consciousness.
The following have also been reported rarely: nystagmus, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea, diarrhoea and CNS and respiratory system depression. In cases of severe poisoning, metabolic acidosis may occur.
There have been reports of disorientation, excitement, fainting and cardiovascular toxicity including hypotension, bradycardia and tachycardia. In cases of significant overdose, renal insufficiency and hepatic damage are possible.

Treatment
There is no specific antidote for an ibuprofen overdose.
In the event of an overdose, a symptomatic and supporting treatment is therefore indicated. Special attention should be paid to monitoring blood pressure, acid-base balance and possible gastrointestinal bleeding.

Administration of activated carbon should be considered within one hour of ingestion of a potentially toxic amount. As an alternative in adults, gastric lavage should be considered within one hour after ingestion of a potentially life-threatening overdose.

Adequate urine output must be assured and renal and hepatic function should be closely monitored.

The patient must remain under observation for at least four hours following ingestion of a potentially toxic amount of the medicinal product.
Any appearance of frequent or prolonged seizures should be treated with intravenous diazepam. Other supporting measures might be required in relation to the patient's clinical conditions.

For more information, contact the local poison centre.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: non-steroidal anti-inflammatory and antirheumatic medicinal products, propionic acid derivatives.
ATC code: M01AE01

Ibuprofen is a synthetic analgesic and anti-inflammatory medicinal product, which also has strong antipyretic activity. Chemically, it is the forebear of phenyl-propionic derivatives. The analgesic activity is non-narcotic and is 8 to 30 times higher than that of acetylsalicylic acid.

Ibuprofen is a potent inhibitor of prostaglandin synthesis and exerts its activity by peripherally inhibiting its synthesis.

Experimental data suggest that ibuprofen may competitively inhibit the effects of low-dose acetylsalicylic acid on platelet aggregation when these two medicinal products are administered concomitantly. In some pharmacodynamics studies, after administration of single 400mg doses of ibuprofen, taken within 8 hours before or 30 minutes after administration of immediate-release acetylsalicylic acid (81mg), there was a decrease in the effect of acetylsalicylic acid on thromboxane formation and platelet aggregation. Although there are uncertainties regarding the extrapolation of these data from the clinical situation, it is impossible to exclude that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid. The occasional ibuprofen use is not likely to result in clinically significant effects (see section 4.5).

5.2 Pharmacokinetic properties

Ibuprofen is well absorbed after oral and rectal administration; taken on an empty stomach, it produces maximum serum levels in humans after about 45 minutes. Administration of equal doses preceded by ingestion of food has revealed slower absorption and the achievement of peak levels in a period of time between a minimum of one and a half hours and a maximum of three hours.
The plasma half life of the molecule is about two hours. Ibuprofen is metabolised in the liver in two inactive metabolites and these, together with unchanged ibuprofen, are excreted by the kidney both as such and as conjugates. Excretion is rapid and serum levels do not show any accumulation signs. 44% of a dose of ibuprofen is recovered in urine in the form of two pharmacologically inert metabolites and 20% in the form of the medicinal product as such.

5.3 Preclinical safety data

LD_{50} in albino mouse is 800 mg/kg per os; while in rats is 1,600 mg/kg per os. Administration of NSAIDs to pregnant rats may cause restriction of foetal ductus arteriosus.

In experiments on animals, chronic and subchronic toxicity of ibuprofen has mainly been shown in the form of lesions and ulceration of the gastrointestinal tract. *In vitro* and *in vivo* studies have shown no clinical relevance of the mutagenic potential of ibuprofen. Studies on rats and mice have not highlighted any evidence of the carcinogenic effects of ibuprofen.

Ibuprofen leads to inhibition of ovulation in rabbits, as well as disrupting the implantation in various animal species (rabbits, rats, mice). Experimental investigations have shown that ibuprofen passes through the placenta; with toxic doses for the mother, an increased incidence of malformations has been observed (e.g. ventricular septal defects).
No further information is available on preclinical data in addition to that already provided in other parts of this Summary of Product Characteristics (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methylparahydroxybenzoate, propylparahydroxybenzoate, citric acid monohydrate, glycerol, **liquid sorbitol, sucrose, sodium benzoate (E211), sunset yellow (E110),** orange essence D717 BBA, polysorbate 80, powdered agar, purified water.

6.2 Incompatibilities

Not known.

6.3 Shelf life

1 year.
Shelf life after first opening: 6 months.

6.4 Special precautions for storage

Store at a temperature not higher than 25°C.

6.5 Nature and contents of container

Multi-dose 100ml PET bottle containing Oral suspension, 20 mg/ml and supplied with 5ml dosing syringe in polypropylene.
Multi-dose 200ml PET bottle containing Oral suspension, 20 mg/ml and supplied with 5ml dosing syringe in polypropylene.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Mylan Italia S.r.l.
Via Vittor Pisani 20
20124 Milan (Italy)

8. MARKETING AUTHORISATION NUMBERS

BRUFEN 20 mg/ml Oral suspension
20 mg/ml oral suspension in 100ml bottle
M.A.: no. 022593228 20 mg/ml oral suspension in 200ml bottle
M.A.: no. 022593230

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 22 May 2012

10. DATE OF REVISION OF THE TEXT

01/08/2026