SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen 400 mg solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 4 mg of ibuprofen.
Each 100 ml bottle contains 400 mg of ibuprofen.
Excipient with known effect:
Each ml of solution contains 9.10 mg of sodium chloride (3.58 mg of sodium).
Each 100 ml bottle contains 910 mg of sodium chloride (358 mg of sodium).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear and colourless to pale yellow solution for infusion, without any particulate matter.
pH: 6.8-7.8
Osmolarity: 310-360 mOsm/L

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ibuprofen is indicated in adults for the short-term symptomatic treatment of acute moderate pain, and for the short-term symptomatic treatment of fever, when administration by intravenous route is clinically justified, when other routes of administration are not possible.

4.2 Posology and method of administration

Posology
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Use should be limited to situations where oral administration is inappropiate. Patients must switch to oral treatment as soon as this is possible.
This medicinal product is indicated for short-term acute treatment only and should not be used for more than 3 days.
Adequate hydration of the patient should be maintained to minimize the risk of possible adverse reactions at renal level.

Adults
The recommended dose is 400 mg of ibuprofen, every 6 to 8 hours as necessary. The recommended maximum daily dose is 2400 mg and should not be exceeded.

Elderly patients
Like with all non-steroidal anti-inflammatory drugs (NSAIDs), precautions should be taken when treating elderly patients, as they are generally more prone to adverse effects (see section 4.4 and 4.8), and are more likely to have renal, hepatic and cardiovascular dysfunction, and to be using concomitant medications. Specifically, it is recommended to administer the lowest effective dose for the shortest duration necessary to control symptoms for this population. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Renal insufficiency
Precautions should be taken when NSAIDs are used in patients with renal insufficiency. In patients with mild or moderate renal impairment the initial dose should be reduced and be kept as low as possible for the shortest duration necessary to control symptoms and renal function monitored. This medicinal product is contraindicated in patients with severe renal insufficiency (see section 4.3).

Hepatic insufficiency
Precautions should be taken when NSAIDs are used in this population although differences in the pharmacokinetic profile have not been observed. Patients with mild or moderate hepatic insufficiency should start the treatment with reduced doses, the dose should be kept as low as possible for the shortest duration necessary and they should be carefully monitored. This medicinal product is contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Paediatric population
This medicinal product should not be used in children and adolescents. The use of Ibuprofen has not been studied in children and adolescents. Therefore, the safety and efficacy have not been established.

Method of administration
For intravenous use. Ibuprofen should only be administered by qualified healthcare professionals in an environment where appropriate equipment is available (during treatment).
The solution should be administered as an intravenous infusion over 30 minutes.

4.3 Contraindications

- Hypersensitivity to the active substance, to other NSAIDs or to any of the excipients listed in section 6.1;
- A history of bronchospasm, asthma, rhinitis, angioedema or urticaria associated with taking acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory drugs (NSAIDs);

- Conditions involving an increased tendency or active bleeding such as thrombocytopenia;
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding);
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy;
- Cerebrovascular or other active bleeding;
- Severe hepatic or renal insufficiency;
- Severe heart failure (NYHA Class IV);
- Severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake);
- Pregnancy, in the last trimester (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 possible time necessary to control symptoms (see section 4.8).
Concomitant use of Ibuprofen with NSAIDs, including cyclooxygenase-2 selective inhibitors (Coxib), should be avoided.
The frequency of the adverse reactions to NSAIDs is increased in elderly patients, especially gastrointestinal bleeding and perforation, which may be fatal (see section 4.8).

Gastrointestinal risks:
GI bleeding, ulceration or perforation, which can be fatal, have been reported during treatment with all NSAIDs 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 (ASA), or other drugs likely to increase the gastrointestinal risk (see below and section 4.5).
Patients with a history of GI toxicity, particularly in the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
Caution should be advised in patients receiving concomitant medications, which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (ASA) (see section 4.5).
When GI bleeding or ulceration occurs in patients receiving Ibuprofen, treatment should be withdrawn (see section 4.3).
NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

Cardiovascular and cerebrovascular effects:

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).

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.

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.

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.

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).

Hepatic or renal insufficiency:

Ibuprofen should be used with caution in patients with a history of liver or kidney disease and especially during simultaneous treatment with diuretics, as the inhibition of prostaglandins can cause fluid retention and renal function impairment. Ibuprofen should be administered in these patients at the lowest dose possible, and patient´s renal function should be regularly monitored.
In case of dehydration, ensure sufficient fluid intake. Use special caution in dehydrated patients, for example due to diarrhea, such as dehydration could be a trigger factor for the development of kidney failure.
Regular use of analgesics, especially when combining of different analgesic substances, can lead to kidney damage with the risk of renal insufficiency (analgesic nephropathy). This risk is higher in the elderly and patients with renal insufficiency, heart failure, liver dysfunction, those taking diuretics or ACE inhibitors. After discontinuing NSAID therapy, patient´s pre-treatment condition is usually restored.
As with other NSAIDs, ibuprofen can cause mild transient increases in some liver function parameters as well as significant increases in transaminases. If there is a significant increase in these parameters, treatment should be discontinued (see section 4.3).

Anaphylactoid Reactions

As standard practice during intravenous infusion, close patient monitoring is recommended, especially at the beginning of the infusion to detect any anaphylactic reaction caused by the active substance or the excipients.
Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are very rarely observed. At the first signs of a hypersensitivity reaction following the administration of Ibuprofen, therapy must be stopped and symptomatic treatment must be established. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Respiratory disorders:

Caution is required if this medicinal product 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 cause bronchospasm, urticaria or angioedema in such patients.

Haematological Effects:

Ibuprofen may temporarily inhibit the blood-platelet function (thrombocyte aggregation), increasing the bleeding time and the risk of haemorrhage.
Ibuprofen should only be used with particular caution in patients receiving ASA to inhibit platelet aggregation (see sections 4.5 and 5.1).
Patients with coagulation disorders or those undergoing surgery should therefore be monitored. Special medical vigilance is required for use in patients immediately after undergoing major surgery.
During prolonged ibuprofen administration, regular checking of liver values, kidney function, and blood counts is required.
Ibuprofen should be used only after strict assessment of the benefit / risk in patients with congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria).

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Caution is required in patients with certain conditions, which may be made worse:

- In patients who react allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of this medicinal product.
- In patients who suffer from hay fever, nasal polyps or chronic obstructive respiratory disorders as an increased risk exists for them of allergic reaction occurring. These may present as asthma attacks (so-called analgesic asthma), Quincke’s oedema or urticaria.

Aseptic Meningitis:

Some cases of aseptic meningitis have been reported with the use of ibuprofen in patients with systemic lupus erythematosus (SLE). Although it is more likely to occur in patients with SLE and related connective tissue diseases, it has also been reported

in some patients who do not have any underlying chronic disease. This therefore, should be taken into account when administering this treatment (see section 4.8).

Ophthalmological Effects:

Blurred or diminished vision, scotomata, and changes in colour vision have been reported with oral ibuprofen. Discontinue ibuprofen if the patient develops such complaints, and refer the patient for an ophthalmologic examination that includes central visual fields and colour vision testing.

Others:

Prolonged use of painkillers may cause headache that must not be treated with increased doses of the medicinal product.

Exceptionally, varicella can cause 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 tubular acidosis and hypokalaemia may occur following acute overdose and in patients receiving ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

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.

Interference with analytical tests:

- bleeding time (may be extended for a day after discontinuation of therapy)
- blood glucose concentration (may decrease)
- creatinine clearance (may decrease)
- haematocrit or haemoglobin (may decrease)
- blood levels of urea nitrogen and serum creatinine and potassium (may increase)
- with liver function tests: increased transaminase values

Precautions regarding excipients:
This medicinal product contains 358 mg sodium per bottle, equivalent to 17.9 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Other NSAIDs, including COX-2 inhibitors and salicylates:
As a result of synergist effects, the concurrent administration use of two or more NSAIDs may increase the risk of gastrointestinal ulcers and bleeding. Co-administration of ibuprofen with other NSAIDs should therefore be avoided (see section 4.4).
Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.
Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid 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).

Lithium:
Co-administration of ibuprofen with lithium-containing medicinal products can increase the serum level of lithium.
Checking the serum lithium level is necessary.

Cardiac glycosides (Digoxin):
NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma levels of cardiac glycosides. Monitoring of serum digoxin is recommended.

Phenytoin:
Plasmatic levels of phenytoin may be increased in the concomitant treatment with ibuprofen and therefore the risk of toxicity may increase.

Antihypertensive (Diuretics, ACE inhibitors, betareceptor blocking medicines and angiotensin-II antagonists:
Diuretics and ACE-inhibitors may increase the nephrotoxicity of NSAIDs. NSAIDs can reduce the effect of diuretics and other antihypertensive drugs, including ACE-inhibitors and beta-blockers. In patients with reduced kidney function (e.g. dehydrated patients or elderly patients with reduced kidney function) the concomitant use of an ACE inhibitor and angiotensin-II antagonists with a cyclo-oxygenase-inhibiting medicinal product can lead to further impairment of kidney function, and to acute renal failure. This is usually reversible. Such combinations should therefore only be used with caution, especially in elderly patients. Patients have to be instructed to drink sufficient liquid. Renal function should be measured after the start of concomitant therapy, and periodically thereafter.
The concomitant administration of ibuprofen and ACE-inhibitors may lead to hyperkalaemia.

Potassium sparing diuretics
Concomitant use may cause hyperkalaemia (check of serum potassium is recommended).

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 (e.g. clopidogrel and ticlopidine) and selective serotonin reuptake inhibitors (SSRIs):
Increased risk of gastrointestinal bleeding (see section 4.4). NSAIDs should not be combined with ticlopidine due to the risk of an additive effect in the inhibition of platelet function.

Methotrexate:
NSAIDs inhibit the tubular secretion of methotrexate and certain metabolic interactions may occur resulting in decreased clearance of methotrexate. The administration of ibuprofen within 24 hours before or after administration of methotrexate may lead to an elevated concentration of methotrexate and an increase in its toxic effect. 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:
The risk of a kidney-damage by ciclosporin is increased by the concomitant administration of certain non-steroidal anti-inflammatory drugs. This effect cannot be ruled out for a combination of ciclosporin and ibuprofen either.

Anti-coagulants:
NSAIDs may enhance the effect of anti-coagulants, such as warfarin (see section 4.4). In case of simultaneous treatment, monitoring of the coagulation state is recommended.

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

Tacrolimus:
Elevated risk of nephrotoxicity.

Zidovudine:
There is evidence of an increased risk of haemarthrosis and haematomas in HIV positive haemophilia patients receiving concurrent treatment with zidovudine and ibuprofen. There may be an increased risk of haematoxicity during concomitant use of zidovudine and NSAIDs.

Probenecid and sulfinpyrazone:
Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.

Quinolone antibiotics:
Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

CYP2C9 Inhibitors:
Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the ibuprofen dose should

be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

Mifepristone:
If NSAIDs are used within 8-12 days after the mifepristone administration, they may decrease the effect of mifepristone.

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.

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

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

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 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 loss 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 (Section 5.3).

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. Although IV ibuprofen is only indicated for up to 3 days treatment, 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;

- may expose the mother and the neonate, at the end of the 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 use is contraindicated during the third trimester of pregnancy (See section 4.3).

Breast-feeding

Ibuprofen and its metabolites can pass in low concentrations into the breast milk. No harmful effects to infants are known to date, so for short-term treatment with lower doses interruption of breast-feeding would generally not be necessary, however it is recommended to interrupt breast-feeding when using higher doses than 1200 mg daily or longer periods due to the potential to inhibit prostaglandin synthesis in the neonate.

Fertility

There is some evidence that drugs, which inhibit cyclo-oxygenase / prostaglandin synthesis, may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

4.7 Effects on ability to drive and use machines

Ibuprofen, in single or short-term use, has no or negligible influence on the ability to drive and use machines. However, the occurrence of relevant undesirable effects such as fatigue and vertigo can impair reactivity, and the ability to drive a vehicle and/or use machines may be reduced. This particularly applies when combined with alcohol.

4.8 Undesirable effects

The following frequencies are taken as a basis when evaluating undesirable effects:

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

Not known: frequency cannot be estimated from the available data

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. Particularly the risk of gastrointestinal bleeding occurring is dependent on the dose range and the duration of use.

Very rarely have been reported severe hypersensitivity reactions (including infusion site reactions, anaphylactic shock) and serious cutaneous adverse reactions such as bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), erythema multiforme and alopecia.

Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of non-steroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the non-steroidal anti-inflammatory drugs.

Photosensitivity, allergic vasculitis and, in exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see section 4.4).

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

Infections and infestations	Very rare	Exacerbation of infection-related inflammations (e.g. development necrotising fasciitis) coinciding with the use of non-steroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the non-steroidal anti-inflammatory drugs.
Blood and lymphatic system disorders	Very rare	Disturbances to blood formation (anaemia, agranulocytosis, leucopenia, thrombocytopenia, and pancytopenia,). First symptoms are: fever, sore throat, superficial mouth wounds, influenza-like complaints, severe lassitude, nosebleeds and skin bleeding.
Immune system disorders	Uncommon	Hypersensitivity reactions with skin rashes and itching, as well as asthma attacks (possibly with drop in blood pressure)
	Very rare	Systemic lupus erythematosus, severe hypersensitivity reactions, face-oedema, swelling of the tongue, swelling of the internal larynx with constriction of the airways, difficulty breathing, palpitations, hypotension and life-threatening shock).
Metabolism and nutrition disorders	Not known	Hypokalaemia[1]
Psychiatric disorders	Uncommon	Anxiety, restlessness
	Rare	Psychotic reactions, nervousness, irritability, confusion or disorientation and depression
Nervous System disorders	Very common	Fatigue or sleeplessness, headache, dizziness
	Uncommon	Insomnia, agitation, irritability or tiredness
	Very rare	Aseptic meningitis (stiff neck, headache, nausea, vomiting, fever or confusion). Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed.
Eye disorders	Uncommon	Visual disturbances
	Rare	Reversible toxic amblyopia
Ear and labyrinth disorders	Common	Vertigo

	Uncommon	Tinnitus
	Rare	Hearing disorders
Cardiac disorders	Very rare	Palpitations, heart failure, myocardial infarction
	Not known	Kounis syndrome
Vascular disorders	Very rare	Arterial hypertension
Respiratory, thoracic and mediastinal disorders	Very rare	Asthma, bronchospasm, dyspnoea and wheezing
Gastrointestinal disorders	Very common	Pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation and slight gastro-intestinal blood losses that may cause anaemia in exceptional cases
	Common	Gastrointestinal ulcers, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn´s disease
	Uncommon	Gastritis
	Rare	Oesophageal stenosis, exacerbation of diverticular disease, unspecific haemorrhagic colitis. If gastrointestinal bleeding occurs could cause anaemia and haematemesis
	Very rare	Oesophagitis, pancreatitis, formation of intestinal, diaphragm-like strictures
Hepatobiliary disorders	Rare	Jaundice, hepatic dysfunction, hepatic damage, particularly in long-term therapy, acute hepatitis
	Not known	Hepatic insufficiency
Skin and subcutaneous tissue disorders	Common	Skin eruption
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)
	Uncommon	Urticaria, pruritus, purpura (including allergic purpura), skin rash
	Very rare	Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis), alopecia. Photosensitivity reactions and allergic vasculitis. In exceptional cases, severe skin infections and soft-tissue complications in varicella infection (see also “Infections and infestations”).
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	Rare	Stiff neck
Renal and urinary disorders	Uncommon	Reduced urinary excretion and formation of oedemas, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis that may be accompanied by acute renal insufficiency.
	Rare	Renal tissue damage (papillary necrosis), particularly in long-term therapy, increased serum uric acid concentration in the blood
	Not known	Renal tubular acidosis[1]
General disorders and administration site conditions	Common	Pain and burning sensation in the administration site

	Not known	Injection site reactions such as swelling, haematoma or bleeding.

[1]-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 the 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

Symptoms

Central nervous system disturbances include headache, confusion, nystagmus, tinnitus, dizziness, light-headedness, unconsciousness, convulsions (mainly in children) and ataxia, as well as abdominal pain, nausea and vomiting, may occur as symptoms of an overdose. In addition, gastrointestinal bleeding, as well as functional disturbances of the liver and kidneys, is possible. There may furthermore be hypotension, hyperkalaemia, hypothermia, respiratory depression and cyanosis.

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

In serious poisoning, metabolic acidosis may occur.

Treatment
Treatment is symptomatic and there is no specific antidote.
The therapeutic possibilities for treatment of intoxication are dictated by the extent, level and clinical symptoms according to the common intensive care practices.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *Anti-inflammatory and antirheumatic products, non-steroids. Propionic acid derivatives. Ibuprofen*
ATC code: *M01AE01*
Ibuprofen is a non-steroidal anti-inflammatory drug that, in conventional animal-experiment inflammation models, has proven to be effective, probably through prostaglandin synthesis inhibition. In humans, ibuprofen has an antipyretic effect, reduces inflammatory-related pain and swelling. Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced 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 pharmacodynamic 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 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 administered intravenously, therefore there is no absorption process and bioavailability of ibuprofen is 100%.
After intravenous administration of ibuprofen in humans, the maximum concentration (Cmax) of S- enantiomer (active) and R-enantiomer is reached at approximately 40 minutes, with a rate of infusion of 30 minutes.

Distribution
The estimated volume of distribution is 0.11 to 0.21 L / kg.
Ibuprofen is extensively bound to plasma proteins, primarily albumin.

Biotransformation
Ibuprofen is metabolised in the liver into two inactive metabolites, and these together with unmetabolized ibuprofen, are excreted by the kidney either as such or as conjugates.
After an oral application, ibuprofen is already partly absorbed in the stomach and then completely in the small intestine. Following hepatic metabolisation (hydroxylation, carboxylation), the pharmacologically inactive metabolites are completely eliminated, mainly renally (90 %), but also with the bile.

Elimination
Excretion by the kidney is rapid and complete. The elimination half-life is about 2 hours.

Linearity / non-linearity
Ibuprofen shows linearity in the area under the curve of plasma concentration-time after a single administration of ibuprofen (in a range of 200 - 800 mg).

Pharmacokinetic / pharmacodynamic relationship(s)
There is a correlation between plasma levels of ibuprofen, its pharmacodynamic properties and overall safety profile. Ibuprofen pharmacokinetics is stereoselective after intravenous and oral administration.
The mechanism of action and pharmacology of intravenous ibuprofen do not differ from the mechanism of oral ibuprofen.

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 have been reported compared with healthy controls.
In end-stage renal disease patients receiving dialysis the mean free fraction of ibuprofen was about 3% compared with about 1% in healthy volunteers. Severe impairment of renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis (see sections 4.3 and 4.4).

Hepatic impairment
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 4.3 and 4.4).

5.3 Preclinical safety data

The subchronic and chronic toxicity of ibuprofen in animal trials showed up mainly in the form of lesions and ulcers in the gastrointestinal tract. In vitro and in vivo studies gave no clinically relevant evidence of the mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found.
Ibuprofen led to an inhibition of ovulation in rabbits and impaired implantation in various animal species (rabbit, rat, mouse). Experimental studies in rats and rabbits have shown that ibuprofen crosses the placenta. Following the administration of maternotoxic doses, an increased incidence of malformations (ventricular septal defects) occurred in the offspring of rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

From a microbiological point of view, the product should be used immediately after opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The primary packaging is a 100 ml LDPE container with Twin-cap in packs of 10 bottles and 20 bottles of 100 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product is indicated for use as a single dose; any unused solution should be discarded. Before administration, the solution should be visually inspected to ensure it is clear and colourless to pale yellow. It should not be used if any particulate matter is observed.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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