SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen 600 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ibuprofen 600 mg film-coated tablets:

Each film-coated tablet contains 600 mg ibuprofen. Excipient(s) with known effect:

Sodium: 2.26 mg/tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Ibuprofen 600 mg film-coated tablets:

White coloured, capsule shaped coated tablets plain on one side and debossed “600” on other side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ibuprofen is indicated for its analgesic and anti-inflammatory effects in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, osteoarthritis and other non-rheumatoid (seronegative) arthropathies. In the treatment of non-articular rheumatic conditions, ibuprofen is indicated in periarticular conditions such as frozen shoulder (capsulitis), bursitis, tendonitis, tenosynovitis and low back pain; Ibuprofen can also be used in soft tissue injuries such as sprains and strains. Ibuprofen is also indicated for its analgesic effect

in the relief of mild to moderate pain such as dysmenorrhoea, dental and post-operative pain and for the symptomatic relief of headache including migraine headache.

4.2 Posology and method of administration

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

Adults and children over 12 years of age : The recommended dosage of ibuprofen is 1200-1800 mg daily in divided doses. Some patients can be maintained on 600-1200 mg daily. In severe or acute conditions, it can be advantageous to increase the dosage until the acute phase is brought under control, provided that the total daily dose does not exceed 2400 mg in divided doses.

In Juvenile Rheumatoid Arthritis, up to 40 mg/kg of body weight daily in divided doses may be taken.

Tablets are not suitable for children under the age of 12 years.

Elderly: The elderly are at increased risk of serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy. If renal or hepatic function is impaired, dosage should be assessed individually.

Renal impairment: Patients with mild to moderate renal impairment, (see section 4.4 - Special warnings and precautions for use) and patients with severe renal insufficiency (see section 4.3 – Contraindications)

Hepatic impairment: For patients with mild to moderate hepatic impairment (see section 4.4 Special warnings and precautions for use) and patients with severe hepatic dysfunction (see section 4.3-Contraindications).

For oral administration. It is recommended that patients with sensitive stomachs take ibuprofen with food. If taken shortly after eating, the onset of action of ibuprofen may be delayed. To be taken preferably with or after food, with plenty of fluid. Ibuprofen tablets should be swallowed whole and not chewed, broken, crushed or sucked on to avoid oral discomfort and throat irritation.

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

4. CLINICAL PARTICULARS

4.3 Contraindications

Ibuprofen is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- previous hypersensitivity reactions (e.g. asthma, rhinitis, urticaria or angioedema) in response to acetylsalicylic acid or other NSAIDs
- history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- severe renal failure or severe hepatic failure (see section 4.4).
- severe heart failure (NYHA Class IV)
- last trimester of pregnancy (see section 4.6)
- significant dehydration (caused by vomiting, diarrhoea or insufficient fluid intake)
- cerebrovascular or other active bleeding
- unclarified blood-formation disturbances
- Ibuprofen should not be given to patients with conditions involving an increased tendency to bleeding.

Ibuprofen is contraindicated in children and adolescents younger than 15 years of age. (See section 4.2).

4. CLINICAL PARTICULARS

4.4 Special warnings and Precautions for Use

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

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

The use of Ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the increased risk of ulceration or bleeding (see section 4.5).
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).
Patients treated with NSAIDs long term should undergo regular medical supervision to monitor for adverse events.
Ibuprofen should only be administered under strict consideration of the benefit-risk ratio in the following conditions:

- Systemic Lupus Erythematosus (SLE) or mixed connective tissue diseases.
- Congenital disturbance of porphyrin metabolism (e.g. acute intermittent porphyria)
- The first and second trimester of pregnancy
- Lactation

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
- 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

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.
Clinical studies suggest that use of ibuprofen, particularly at a high doses (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. $\leq$ 1200 mg daily) 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 skin reactions

Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8). Most of these reactions occurred within the first month. If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).
Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Ibuprofen in case of varicella.

Renal effect

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. Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration. There is a risk of renal impairment especially in dehydrated children, adolescents and the elderly.
As with other NSAIDs, 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.

Hepatic:

Hepatic dysfunction (see sections 4.2, 4.3 and 4.8).

SLE and mixed connective tissue disease

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue diseases there may be an increased risk of aseptic meningitis (see below and section 4.8).

Aseptic meningitis

Symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed.
Aseptic meningitis has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Other precautions
Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of hypersensitivity reaction after taking/administering ibuprofen therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Respiratory disorders and hypersensitivity reactions
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 since NSAIDs have been reported to precipitate bronchospasm, urticaria or angioedema in such patients.

Ibuprofen may mask the signs or symptoms of an infection (fever, pain and swelling). 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/ analgesic medications. Patients with medication overuse headache should not be treated by increasing the dose of the analgesic. In such cases the use of analgesics should be discontinued.
In general, the habitual intake of analgesics, particularly the combination use of different analgesic substances, may cause permanent renal damage and a risk of renal failure (analgesics nephropathy).
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.
The concomitant consumption of excessive alcohol with NSAIDs, including ibuprofen may increase the risk of adverse effects on the gastrointestinal tract, such as GI haemorrhage or the central nervous system, possibly due to an additive effect.

Masking of symptoms of underlying infections

Ibuprofen tablets 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 **bacteria complications** to varicella. When Ibuprofen tablets 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.

Haematological effects

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

Impaired female fertility

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

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

Cardiac, renal and hepatic impairment

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

Paediatric population

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

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4. CLINICAL PARTICULARS

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of ibuprofen and the following substances should be avoided:

Acetylsalicylic acid:

"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 cardio protective 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).

Cardiac glycosides:

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

Other NSAIDs including cyclooxygenase- 2 selective inhibitors:

As a result of synergistic effects, the concurrent use of several NSAIDs can increase the risk of gastrointestinal ulcers and haemorrhage. Co-administration of ibuprofen with other NSAIDs should therefore be avoided as this may increase the risk of adverse effects (see section 4.4).

Anti-coagulants:

NSAIDs may enhance the effects of anticoagulants, such as warfarin or heparin (see section 4.4).

In case of simultaneous treatment, monitoring of the coagulation state is recommended.

Methotrexate:

NSAID inhibits 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.

Ibuprofen (like other NSAIDs) should be taken only with caution in combination with the following substances:

Digoxin, phenytoin and lithium:

Co-administration of ibuprofen with digoxin, phenytoin or lithium preparations can increase the serum level of these medicinal products. Checking the serum lithium level, serum digoxin and serum phenytoin levels is generally not required on correct use (over 3 or 4 days maximum). Decreases elimination of lithium.

Diuretics beta-blockers and antihypertensives:

NSAIDs can reduce the effect of diuretics and antihypertensives, including ACE-inhibitors, beta- blockers and angiotensin-II receptor antagonists. Diuretics can also increase the risk of nephrotoxicity of NSAIDs. In patients with reduced kidney function (e.g. dehydrated patients or elderly patients with reduced kidney function), the concomitant use of an ACE inhibitor, beta blocker or angiotension II antagonist with a cyclooxygenase-inhibiting medicinal product can lead to further impairment of kidney function and through to acute renal failure. This is usually reversible. Such combination should therefore only be used with caution, especially in elderly patients. The patients have to be instructed to drink sufficient liquid and periodic monitoring of the kidney values should be considered for the time immediately after the start of the combination therapy.
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.

Aminoglycosides:

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

Selective serotonin reuptake inhibitors (SSRIs):

Increased risk of gastrointestinal bleeding (see section 4.4).

Ciclosporine:

The risk of kidney damage by ciclosporin (nephrotoxicity) is increased by the concomitant administration of certain NSAIDs. This effect cannot be ruled out for the combination of ciclosporine and ibuprofen, either.

Cholestyramine:

. The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.

Tacrolimus:

Elevated risk of nephrotoxicity.

Zidovudine:

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

Blood counts 1-2 weeks after starting use together are recommended.

Ritonavir:

May increase the plasma concentrations of NSAIDs.

Mifepristone:

A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs. Limited evidence suggests that coadministration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy.

Probenecid or sulfinpyrazone:
May cause a delay in the elimination of ibuprofen. The uricosuric action of these substances is decreased.

Herbal extracts:

Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

CYP2C9 Inhibitors:

Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors) an increased S (+) ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

Quinolone antibiotics:

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

Sulphonylureas:

NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

Corticosteroids:

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

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) (e.g. clopidogrel and ticlopidine):

Increase the risk of gastrointestinal bleeding (see section 4.4).

Alcohol, bisphosphonates and oxpentifylline (pentoxyflline):

May potentiate the GI side-effects and the risk of bleeding and ulceration.

Baclofen:

Elevated baclofen toxicity.

4. CLINICAL PARTICULARS

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. 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 <x> for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction (see above); which may progress to renal failure with oligo-hydramniosis; the mother and the neonate, at the end of pregnancy to prostaglandin synthesis inhibitors may expose the mother and the neonate to the following:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, ibuprofen is contraindicated during the last trimester of pregnancy.

Breastfeeding

In the limited studies so far available, NSAIDs can appear in the breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding. See section 4.4 Special warnings and precautions for use, regarding female fertility.

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 investigation of infertility, withdrawal of ibuprofen should be considered.

4. CLINICAL PARTICULARS

4.7 Effects on ability to drive and use machines

Ibuprofen generally has no adverse effects on the ability to drive and use machinery. Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery. This effect is potentiated by simultaneous consumption of alcohol.

4. CLINICAL PARTICULARS

4.8 Undesirable effects

With the following adverse drug reactions, it must be accounted for that they are predominantly dose- dependent and vary inter individually. 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, heamatemesis, ulcerative stomatits, gastrointestinal haemorrhage, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis duodenal ulcer, gastric ulcer and gastrointestinal perforation has been observed.

Cardiac disorders and vascular disorders: 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).
Oedema, hypertension, and cardiac failure have been reported in association with NSAID treatment.
Immune system disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and very rarely, erythema multiforme, bullous dermatoses (including Stevens-Johnson syndrome and toxic epidermal necrolysis).
Infections and infestations: Rhinitis and aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).
Exacerbation of infection-related inflammations coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of Ibuprofen the patient is therefore recommended to go to a doctor without delay.
Skin and subcutaneous tissue disorders: In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations").
The following adverse reactions possibly related to ibuprofen and displayed by MedDRA frequency convention and system organ classification. Frequency groupings are classified according to the subsequent conventions. Assessment of adverse reactions is normally based on the following occurrence frequency:
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 (cannot be estimated from the available data).

System organ class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Rhinitis
	Rare	Meningitis aseptic (see section 4.4)
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia , haemolytic anaemia
Immune system disorders	Uncommon	Hypersensitivity
	Rare	Anaphylactic reaction
Psychiatric disorders	Uncommon	Insomnia, anxiety
	Rare	Depression, confusional state
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Paraesthesia, somnolence
	Rare	Optic neuritis
Eye disorders	Uncommon	Visual impairment
	Rare	Toxic optic neuropathy
Ear and labyrinth disorders	Uncommon	Hearing impaired , tinnitus, vertigo
Respiratory, thoracic and mediastinal disorders	Uncommon	Asthma, bronchospasm, dyspnoea
Gastrointestinal disorders	Common	Dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, 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 disorders	Uncommon	Hepatitis, jaundice, hepatic function abnormal
	Very Rare	Hepatic failure
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Urticaria, pruritus, purpura, angioedema, photosensitivity reaction
	Very rare	Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis,

		Stevens- Johnson syndrome, and toxic epidermal necrolysis)
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalized exanthematous pustulosis (AGEP)
Renal and urinary disorders	Uncommon	Nephrotoxity in various forms e.g.Tubulointerstitial nephritis, nephrotic syndrome and renal failure
	Not known	Renal tubular acidosis*
General disorders and administration site conditions	Common	Fatigue
	Rare	Oedema
Cardiac disorders	Very rare	Cardiac failure, myocardial infarction (also see section 4.4)
	Not known	Kounis Syndrome
Vascular disorders	Very rare	Hypertension
Metabolism and Nutritional Disorders	Not known	Hypokalaemia*

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

4. CLINICAL PARTICULARS

4.9 Overdose

Symptoms

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours.

The most frequently reported symptoms of overdose include nausea, vomiting, abdominal pain, lethargy and drowsiness. Central nervous system (CNS) effects include headache, tinnitus, dizziness, convulsion,

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

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.

Toxicity

Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults. However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400 mg/kg or greater.

Treatment

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose. Good urine output should be ensured. Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient’s clinical condition.

Bronchodilators should be given for asthma. No specific antidote is available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivatives. ATC code: M01AE01

Ibuprofen is a NSAID that possesses anti-inflammatory, analgesic and antipyretic activity. Animal models for pain and inflammation indicate that ibuprofen effectively inhibits the synthesis of prostaglandins. In humans, ibuprofen reduces pain possibly caused by inflammation or connected with it, swelling and fever. Ibuprofen exerts an inhibitory effect on prostaglandin synthesis by inhibiting the activity of cyclo-oxygenase. In addition, ibuprofen has an inhibitory effect on ADP (adenosine diphosphate) or collagen stimulated 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 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).

Ibuprofen inhibits prostaglandin synthesis in the uterus, thereby reducing intrauterine rest and active pressure, the periodic uterine contractions and the amount of prostaglandins released into the circulation. These changes are assumed to explain the alleviation of menstrual pain. Ibuprofen inhibits renal prostaglandin synthesis which can lead to renal insufficiency, fluid retention and heart failure in risk patients (see section 4.3).

Prostaglandins are connected with ovulation and the use of medicinal products inhibiting prostaglandin synthesis may therefore affect the fertility of women (see section 4.4, 4.6 and 5.3).

5.2 Pharmacokinetic properties

Absorption

Ibuprofen is rapidly absorbed from the gastrointestinal tract, peak serum concentrations occurring 1-2 hours after administration.

Distribution

Ibuprofen is rapidly distributed throughout the whole body. The plasma protein binding is approximately 99%.

Biotransformation

Ibuprofen is metabolised in the liver (hydroxylation, carboxylation).

Elimination

The elimination half-life is approximately 2.5 hours in healthy individuals. Pharmacologically inactive metabolites are mainly excreted (90%) by the kidneys but also in bile.

5.3 Preclinical safety data

As a well-established and widely used product, the pre-clinical safety of ibuprofen is well documented.

Ibuprofen's sub chronic and chronic toxicity was mainly shown by animal tests as gastric tract damage and ulcers.

The vitro and in vivo tests have not shown any clinically significant signs about ibuprofen's mutagenicity. Furthermore, no carcinogenic effects have been observed in mice and rats.

Ibuprofen inhibits ovulation in rabbits and impairs implantation in various animal species (rabbit, rat, and mouse). In reproduction tests undertaken with rats and rabbits, ibuprofen passed across the placenta. When using doses toxic to the mother, malformations occur more frequently (i.e. ventricular septum defects).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch B

Sodium lauryl sulfate

Colloidal silicon dioxide

Croscarmellose sodium

Povidine

Microcrystalline Cellulose

Talc

Stearic acid

Opadry White (macrogol (peg) polyvinyl alcohol graft copolymer, talc, titanium dioxide, gmcc type 1 /mono/diglycerides/glycerol of FA, polyvinyl alcohol-part. hydrolyzed)

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original pack.

6.5 Nature and contents of container

Ibuprofen film-coated tablets are packaged in clear PVC/PVDC – Aluminium foil blister pack.

Pack sizes:

Blisters: 48, 84 & 96 film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Special Concept Development (UK) Limited T/A RxFarma Colonial Way,

Watford, Hertfordshire WD24 4YR

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36722/0223

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/06/2024

10 DATE OF REVISION OF THE TEXT

21/05/2026