1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen film coated Tablets BP 400mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 400mg of Ibuprofen BP.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pink, film coated, round, biconvex tablets, with "C4" on one side and no inscription on the other side

4.1. Therapeutic Indications

Ibuprofen is indicated for symptomatic treatment of pain and inflammation in arthritic diseases (e.g. rheumatoid arthritis) degenerative arthritic conditions (e.g. osteoarthritis), and in painful swelling and inflammation after soft tissue injuries.

It is also indicated for the relief of mild to moderate pain, e.g. primary dysmenorrhea and fever.

Ibuprofen is also indicated for the Symptomatic treatment of migraine.

4.2 Posology and method of administration

Undesirable effects may be minimised by using The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4). The treating physician decides on the duration of treatment.

In rheumatic diseases the use of ibuprofen can be required for a longer period.

The ibuprofen dose depends on the patient's age and body weight. The maximum single dose for adults should not exceed 800 mg of ibuprofen.

Posology

Mild to moderate pain and fever

Adults and adolescents ≥40 kg body weight (12 years and above):
200-400 mg given as a single dose or 3-4 times a day with an interval of 6 hours as required. The dosage in migraine headache should be: 400 mg given as a single dose, if necessary 400 mg with intervals up to 6 hours.
The maximum daily dose should not exceed 1200 mg.

Paediatric population
Children ≥20 kg body weight (6-11 years):
Children 20-29 kg (6-9 years): 200 mg 1-3 times a day with intervals of 6 hours as required.
The maximum daily dose should not exceed 600 mg.

Children 30-90 kg (10-11 years):
200 mg 1-4 times a day with intervals of 6 hours as required.
The maximum daily dose should not exceed 800 mg.

Ibuprofen is contraindicated in children below 20 kg body weight or younger than 6 years of age. (See section 4.3)

Primary dysmenorrhoea

Adults and adolescents ≥40 kg body weight (12 years of age and above):
200-400 mg 1-3 times a day, with an interval up to 6 hours, as needed. The maximum daily dose should not exceed 1200 mg.

Rheumatic diseases

Adults:
The recommended dose is 1200-1800 mg daily in divided doses. Maintenance doses of 600 mg-1200 mg daily may be effective in some patients. In acute and severe conditions the dose may be (temporarily) increased to a maximum of 2400 mg in 3 or 4 divided doses.

Adolescents from 15 to 17 years of age:
The recommended dose should be adjusted by weight: 20 mg/kg to a maximum of 40 mg/kg body weight daily (max 2400 mg daily) in 3 to 4 divided doses.

Elderly:

NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events and are at increased risk of potentially fatal gastrointestinal haemorrhage, ulceration or perforation (see section 4.4). If treatment is considered necessary, the lowest dose for the shortest duration necessary to control symptoms should be used. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Impaired renal function
In patients with mild or moderate reduction of renal function, the dose should be kept as low as possible for the shortest duration necessary to control symptoms and renal function monitored. (For patients with severe renal failure see section 4.3).

Impaired liver function
In patients with mild or moderate reduction of liver function the dose should be kept as low as possible for the shortest duration necessary to control symptoms and liver function monitored. (For patients with severe liver failure see section 4.3).

Method of administration

The tablet should be swallowed with a glass of water preferably after a meal. It is recommended, that patients with a sensitive stomach take ibuprofen during a meal.

4.3 Contraindications

Ibuprofen should not be given to patients:

- with active or history of recurrent peptic ulceration/haemorrhage (two or more distinct episodes of proved ulceration or bleeding)
- with a hypersensitivity to ibuprofen or to any of the excipients listed in section 6.1
- with previous hypersensitivity reactions (e.g. asthma, rhinitis, urticaria or angioedema) in response to acetylsalicylic acid or other NSAIDs
- with a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- with severe heart failure (NYHA Class IV)
- severe hepatic failure and severe renal failure (see section 4.4)
- during the 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 is contraindicated in children below 20 kg body weight or younger than 6 years of age (see section 4.2).

4.4 Special warnings and precautions for use

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).

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

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)

Renal Effects:

Ibuprofen may cause the retention of sodium, potassium and fluid in patients who have not previously suffered from renal disorders because of its effect on renal perfusion. This may cause oedema or even lead to cardiac insufficiency or hypertension in predisposed patients.
As with other NSAIDs, the prolonged administration of ibuprofen to animals has resulted in renal papillary necrosis and other pathological renal changes. In humans, there have been reports of acute interstitial nephritis with haematuria, proteinuria and occasionally nephrotic syndrome. Cases of renal toxicity have also been observed in patients in whom prostaglandins play a compensatory role in the maintenance of renal perfusion. In these patients, administration of NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of suffering this reaction are those with renal dysfunction, heart failure, hepatic dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID treatment is generally followed by recovery to the pre-treatment state.

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

Hepatic:

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

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 and oedema have been reported in association with NSAID therapy.

Clinical trial data suggest that use of ibuprofen, particularly at a high dose (2400mg daily) and in long-term treatment 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. ≤1200mg daily) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA IIIII), 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 be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (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 Tablet. 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.

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 aspirin, or other drugs 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 and heparin, selective serotonin-reuptake inhibitors or antiplatelet agents such as aspirin (see section 4.5).

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

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn’s disease) as these conditions may be exacerbated (see section 4.8).

SLE and mixed connective tissue disease:

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

Dermatological:
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 very rarely in association with the use of Ibuprofen(see section 4.8).Most of the reaction occurred within the first month of treatment. 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.

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 bacterial complications to varicella. When Ibuprofen Tablets 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.

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.

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

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

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

In general 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.

Consumption of alcohol should be avoided since it may intensify side effects of NSAIDs, especially if affecting the gastrointestinal tract or the central nervous system.
Patients on ibuprofen should report to their doctor signs or symptoms of gastro-intestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain or oedema.

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

Ibuprofen 400mg film-coated Tablets contain sodium:
This medicine contains less than 1mmol sodium (23mg) per 400mg film-coated tablets, that is to say essentially ‘sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients.

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).

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 (see section 4.4).

Ibuprofen (like other NSAIDs) should be taken only with caution in combination with the following substances:
Diuretics and antihypertensives:
NSAIDs can reduce the effect of diuretics and antihypertensives, including ACE-inhibitors, beta-blockers and angiotensin-II antagonists. 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.

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.

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 is necessary and it is recommended to check the serum digoxin and serum phenytoin levels.

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

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

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

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

Quinolone antibiotics:
Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Selective serotonin reuptake inhibitors (SSRIs):
Increased risk of gastrointestinal bleeding (see section 4.4).

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

Tacrolimus:
Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

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 haematotoxicit 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.

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.

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

Anti-platelet aggregation agents (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.

4.6 Fertility, pregnancy and lactation

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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 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, (see above) the mother and the neonate, at the end of pregnancy to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently Ibuprofen is contraindicated during the last trimester of pregnancy. (see sections 4.3 and 5.3)

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

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

4.7 Effects on ability to drive and use machines

Ibuprofen generally has no adverse effects on the ability to drive and use machinery. However since at high dosage side effects such as fatigue, somnolence vertigo (reported as common) and visual disturbances (reported as uncommon) may

be experienced, the ability to take part actively in road traffic or operate machinery may be impaired in individual cases. This effect is potentiated by simultaneous consumption of alcohol

4.8 Undesirable effects

With the following adverse drug reactions, it must be accounted for that they are predominantly dose- dependent and vary interindividually.

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, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

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

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

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
Blood and lymphatic system disorders	Very rare	Haematopoietic disorders (anaemia, leucopoenia, thrombocytopenia, pancytopenia, agranulocytosis, neutropenia). The first symptoms or signs may include: fever, sore throat, surface mouth ulcers, flu-like symptoms, severe fatigue, nasal and skin bleeding

Immune system disorders	Uncommon	Hypersensitivity reactions such as urticaria, pruritus, purpura and exanthema as well as asthma attacks (sometimes with hypotension)
	Rare	Lupus erythematosus syndrome
	Very rare	Severe hypersensitivity reactions. The symptoms may include: facial oedema, swelling of the tongue, internal laryngeal swelling with constriction of the airways, dyspnoea, tachycardia, fall of blood pressure to the point of life- threatening shock
Psychiatric disorders	Rare	Depression, confusion, hallucinations
	Not known	Anxiety
Nervous system disorders	Common	Headache, somnolence, vertigo, fatigue, agitation, dizziness, insomnia, irritability
	Very rare	Aseptic menigitis
	Not known	Optic neuritis, paraesthesias
Eye disorders	Uncommon	Visual disturbances
	Rare	Toxic amblyopia
Ear and labyrinth disorders	Very rare	Tinnitus
	Not known	Hearing impaired
Cardiac disorders	Very rare	Palpitations, heart failure, myocardial infarction, acute pulmonary Oedema, oedema
	Not Known	Kounis syndrome
Vascular disorder	Very rare	Hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinitis, bronchospasm

Gastrointestinal disorders	Very common	Gastrointestinal disorders, such as heartburn, dyspepsia, abdominal pain and nausea, vomiting, flatulence, diarrhoea, constipation
	Common	Gastrointestinal ulcers, sometimes with bleeding and perforation (see section 4.4), occult blood loss which may lead to anaemia, melaena, haematemesis, ulcerative stomatitis, colitis, exacerbation of inflammatory bowel disease, complications of colonic diverticula (perforation, fistula)
	Uncommon	Gastritis
	Very rare	Oesophagitis, pancreatitis, intestinal strictures
Hepatobiliary disorders	Very rare	Liver dysfunction, liver damage, especially in long-term use, liver failure, acute hepatitis, jaundice
Skin and subcutaneous tissue disorders	Very rare	Severe cutaneous adverse reactions(SCARs)(including Erythema multiforme, exfoliative dermatitis, bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, alopecia, necrotising fascitis)
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP); photosensitivity reactions
Renal and urinary disorders	Uncommon	Development of oedema especially in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis which can be associated with renal failure
	Rare	Renal papillary necrosis in long-term use (see section 4.4)
	Very rare	Acute renal failure

	Not known	Ureteric colic, dysuria Renal tubular acidosis*
Metabolism and Nutrition Disorders	Not known	Decreased Appetite Hypokalaemia*
General disorders and administration site conditions	Not known	Malaise
Investigations	Rare	Increase of blood urea nitrogen, serum transaminases and alkaline phosphatase, decrease in haemoglobin and haematocrit values, inhibition of platelet aggregation, Prolonged bleeding time, decrease of serum calcium, increase in serum uric acid

Description of Selected Adverse Reactions

*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.

4.9. Overdose

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Nystagmus, blurred vision, tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as vertigo, dizziness, drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. Children may also develop myoclonic cramps. In serious poisoning metabolic acidosis may occur, hypothermia and hyperkalaemia may also occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of

circulating clotting factors. Acute renal failure liver damage hypotension, respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Treatment
Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Gastric emptying oral administration of activated charcoal is indicated if the patient presents within 1 hour of ingestion of more than 400 mg per kg of body weight. If ibuprofen has already been absorbed, alkaline substances should be administered to promote the excretion of the acid ibuprofen in the urine. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Bronchodilators should be given for asthma. No specific antidote is available.

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).

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 aspirin on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81 mg), a decreased effect of ASA 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

Pregelatinised starch,
Maize starch,
Colloidal anhydrous silica,
Magnesium stearate,
Methylhydroxypropylcellulose,
Polyethylene glycol 6000,
Titanium dioxide(E171),
Dioctyl sodium sulphosuccinate,
Erythrosine lake (E127)

6.2 Incompatibilities

None known.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Protect from light. Store below 25°C.

6.5 Nature and contents of container

Polypropylene containers with a low density polyethene tamper evident lid, containing either 21, 100, 250, 500 or 1000 tablets.

Packs of 5000 and 10,000 tablets for bulk supply (supplied in polybags, free from additives inside a cardboard outer container).

PVC/PVDC- ALU blister containing 84 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
Key House, Sarum Hill, Basingstoke, RG21 8SR,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0684

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

16/12/2024