

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen Zentiva 400 mg film-coated tablets

Ibuprofen Zentiva 600 mg film-coated tablets

Ibuprofen Zentiva 800 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each <Product name> 400 mg film-coated tablet contains ibuprofen 400 mg.

Each <Product name> 600 mg film-coated tablet contains ibuprofen 600 mg.

Each <Product name> 800 mg film-coated tablet contains ibuprofen 800 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

<Product name> 400 mg film-coated tablet: white to off-white rounded film-coated tablets with diameter 12 mm.

<Product name> 600 mg film-coated tablet: white to off-white oblong (17 x 10 mm) film-coated tablets.

<Product name> 800 mg film-coated tablet: light yellow to beige oblong (20 x 10 mm) film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[<Product name> 400 mg, 600 mg and 800 mg film-coated tablets]

Rheumatic conditions such as arthritic diseases (e.g. rheumatoid arthritis including juvenile rheumatoid arthritis), non-articular rheumatic conditions, other muscular and joint disorders, and soft tissue injuries.

<Product name> 400 mg and 600 mg is recommended for adults and adolescents from 40 kg bodyweight (over 12 years).

800 mg <Product name> is recommended for adults only (see section 4.2).

[<Product name> 400 mg film-coated tablets]

In addition, <Product name> 400 mg is intended for short-term symptomatic treatment of mild to moderate pain, migraine, primary dysmenorrhea and/or fever.

4.2 Posology and method of administration

Posology

The treatment should start with the lowest dose anticipated to be effective, which can subsequently be adjusted, depending on the therapeutic response and any undesirable effects.

The maximum single dose should not exceed 800 mg of ibuprofen for adults and 600 mg of ibuprofen for adolescents.

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

Rheumatic conditions

In long-term treatment of rheumatic conditions, a low maintenance dose should be the aim.

[<Product name> 400 mg, 600 mg and 800 mg film-coated tablets]

Adults:

The usual dose is 400-600 mg 3 times a day with an interval of at least 4 to 6 hours. Maintenance doses of 600 mg-1 200 mg daily may be effective in some patients. In acute and severe conditions, the dose may be increased to a maximum of 2 400 mg divided in 3 doses of 800 mg or 4 doses of 600 mg.

Adolescents from 40 kg bodyweight (over 12 years of age):

The recommended dose is 20 mg/kg to a maximum of 40 mg/kg body weight daily with maximum daily dose 2 400 mg divided in 3 to 4 doses of 400 mg or 600 mg.

[<Product name>400 mg film-coated tablets]

Mild to moderate pain and acute pain and fever associated with the common cold

Adults and adolescents from 40 kg bodyweight (older than 12 years):

400 mg given as a single dose or 3 times a day with an interval of at least 4 to 6 hours. The dosage in migraine headache should be: 400 mg given as a single dose, if necessary 400 mg with intervals of 4 to 6 hours.

The maximum daily dose should not exceed 1 200 mg.

Primary dysmenorrhoea

Adults and adolescents from 40 kg bodyweight (over 12 years of age):

400 mg 1-3 times a day, with an interval of at least 4-6 hours, as needed. Treatment is started at the first sign of menstruation problems. The maximum daily dose should not exceed 1 200 mg.

Paediatric population:

The ibuprofen dose in children and adolescents depends on the patient's age and body weight.

<Product name> 400 mg and 600 mg is not to be used in adolescents weighing less than 40 kg or children below 12 years of age.

<Product name> 800 mg is not to be used in children and adolescents under 18 years of age.

Special populations

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.

Renal impairment

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. (This medicinal product is contraindicated in patients with severe renal failure, see section 4.3).

Hepatic impairment

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. (This medicinal product is contraindicated in patients with severe hepatic failure, see section 4.3).

Method of administration

The tablet should be swallowed with a glass of water.

The tablets should not be crushed, chewed or sucked to avoid stomach or throat irritation.

It is recommended that patients with a sensitive stomach take <Product name> with food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- History of hypersensitivity reactions (e.g. bronchospasm, asthma, rhinitis, angioedema or urticaria) associated with the intake of acetylsalicylic acid (ASA) or other non-steroidal antiinflammatory drugs (NSAIDs).
- In patients with blood clotting disorders and conditions involving an increased tendency to bleed.
- Active or history of recurrent or existing 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.
- Disorders of haemopoiesis.
- Severe hepatic failure or severe renal failure.
- Severe heart failure (NYHA Class IV).
- During the third trimester of pregnancy (see section 4.6).
- Patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

4.4 Special warnings and precautions for use

The use of ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors increases risk of adverse reactions and should be avoided.

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

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see 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 other autoimmune 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.
- 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 trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2 400 mg 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. $\leq 1\ 200$ mg daily) is associated with an increased risk of myocardial infarction.

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 (2 400 mg/day) should be avoided.

Careful consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking), particularly if high doses of ibuprofen (2 400 mg/day) are required.

Cases of Kounis syndrome have been reported in patients treated with <Product name>. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive

reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Severe cutaneous adverse reactions (SCARs)

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

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.

Masking of symptoms of underlying infections

<Product name> 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 <Product name> 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 (e.g. anaphylactic shock) are observed very rarely. At the first signs of hypersensitivity reaction after taking/administering <Product name> 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.

Prolonged use of any type of analgesics 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). This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore it should be avoided.

During treatment with ibuprofen, some cases with symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed in patients with existing autoimmune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

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

In case of long-term treatment with ibuprofen a periodical monitoring of hepatic and renal function as well as the blood count is necessary, especially in high risk patients.

Concomitant 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.

<Product name> contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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, low dose: Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1). Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

Other NSAIDs, including salicylates: 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).

Anticoagulants: 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.

Ticlopidin: NSAIDs should not be combined with ticlopidine due to a risk of an additive effect in the inhibition of the platelet function.

Methotrexate: NSAID inhibits the tubular secretion of methotrexate and certain metabolic interactions can occur resulting in decreased clearance of methotrexate. Accordingly, in high-dose treatment with methotrexate one should always avoid prescribing NSAIDs (see below).

Cardiac glycosides (e.g digoxin): NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma levels of cardiac glycosides. Monitoring of serum digoxin is recommended.

Mifepristone: If NSAIDs are used within 8-12 days after mifepristone administration they can reduce the effect of mifepristone.

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

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.

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

Moclobemide: Enhances the effect of ibuprofen.

Phenytoin, lithium: Co-administration of ibuprofen with 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 phenytoin levels.

Diuretics and antihypertensives: Diuretics and ACE-inhibitors can increase the nephrotoxicity of NSAIDs. NSAIDs can reduce the effect of diuretics and other antihypertensives, 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 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 is increased by the concomitant administration of certain NSAIDs. This effect can not be ruled out for the combination of ciclosporine and ibuprofen, either.

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: Elevated risk of nephrotoxicity.

Methotrexate: The risk of a potential interaction between an NSAID and methotrexate should also be taken into account in connection with low-dose treatment with methotrexate, especially in patients with renal impairment. Whenever combination treatment is given, renal function should be monitored.

Caution should be exercised if both an NSAID and methotrexate are given within 24 hours, as the plasma levels of methotrexate can increase, resulting in increased toxicity (see above).

Ritonavir: May increase the plasma concentrations of NSAIDs.

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

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.

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

Anti-platelet aggregation agents (e.g. clopidogrel): Increase the risk of gastrointestinal bleeding (see section 4.4).

Alcohol, bisphosphonates and oxpentifylline (pentoxifylline): May potentiate the GI side-effects and the risk of bleeding and ulceration.

Baclofen: Elevated baclofen toxicity.

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.

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 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 oligo-hydroamniosis (see above);
- 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 is contraindicated during the third trimester of pregnancy (see section 4.3).

Breast-feeding

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

There is some evidence that drugs, which inhibit cyclooxygenase/prostaglandin synthesis, may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment (see section 4.4). 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

As central nervous undesirable effects such as tiredness and dizziness may occur on use of ibuprofen at higher dosage, the ability to react and the ability to take part actively in road traffic and to operate machines may be impaired in isolated cases. This applies to a greater extent in combination with alcohol.

4.8 Undesirable effects

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

Undesirable effects are mostly dose-dependent. Especially the risk for the occurrence of gastrointestinal bleedings depends on the dosage range and duration of the treatment.

The following table summarises adverse drug reactions of ibuprofen divided into groups according to MedDRA terminology together with their frequency: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ 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	Very rare	Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of nonsteroidal antiinflammatory drugs has been described. This is possibly associated with the mechanism of action of the nonsteroidal antiinflammatory drugs. The symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness clouding have been observed under ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed.
Blood and lymphatic system disorders	Very rare	Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). The first symptoms or signs may include: fever, sore throat, surface mouth ulcers, flu-like symptoms, severe fatigue, nasal and skin bleeding
	Not known	Neutropenia
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
	Very rare	Psychotic reactions
	Not known	Anxiety
Nervous system disorders	Common	Headache, somnolence, vertigo, fatigue, agitation, dizziness, insomnia, irritability
	Very rare	Aseptic meningitis
	Not known	Optic neuritis, paraesthesia
Eye disorders	Uncommon	Visual disturbances
	Rare	Toxic amblyopia
Ear and labyrinth disorders	Very rare	Tinnitus
	Not known	Hearing impaired
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 colitis and Crohn's 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	Uncommon	Photosensitivity, skin rashes
	Very rare	Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, bullous reactions including Stevens-Johnson syndrome, and toxic epidermal necrolysis), alopecia, necrotising fasciitis. In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP)
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
	Very rare	Renal papillary necrosis in long-term use (see section 4.4)
General disorders and administration site conditions	Not known	Malaise
Cardiac disorders	Very rare	Palpitations, heart failure, myocardial infarction, acute pulmonary oedema, oedema
	Not known	Kounis syndrome
Vascular disorders	Very rare	Hypertension, vasculitis
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
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Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high dose (2 400 mg daily) and in long term treatment 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Toxicity

Risk of symptoms at doses >80–100 mg/kg. At doses >200 mg/kg there is a risk of severe symptoms, though with considerable variations between individuals. A dose of 560 mg/kg in a child aged 15 months gave severe intoxication, 3.2 g in a 6-year-old mild to moderate intoxication, 2.8–4 g in a 1½-year-old and 6 g in a 6-year-old severe intoxication even after gastric lavage, 8 g in an adult moderate intoxication and >20 g in an adult very severe intoxication. 8 g administered to a 16-year-old affected the kidney and 12 g in combination with alcohol administered to a teenager resulted in acute tubular necrosis.

Symptoms

The predominant symptoms are ones from the gastrointestinal tract, e.g. nausea, abdominal pains, vomiting (possibly blood-streaked), and headache, tinnitus, confusion and nystagmus. At high doses loss of consciousness, convulsions (mainly in children). Bradycardia, fall in blood pressure. Metabolic acidosis, hypernatraemia, kidney effects, haematuria. Possibly liver effects. Hypothermia and ARDS have occasionally been reported.

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

Treatment

If warranted, gastric lavage, carbon. In the event of gastrointestinal problems, antacids. In the event of hypotension intravenous fluid and if required inotropic support. Ensure adequate diuresis. Correction of acid-base and electrolyte disorders. Other symptomatic therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiinflammatory and antirheumatic products, propionic acid derivatives, ATC code: M01AE01

Ibuprofen is a NSAID that possesses antiinflammatory, 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 pharmacodynamics 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).

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 sections 4.4, 4.6 and 5.3).

5.2 Pharmacokinetic properties

Absorption

Ibuprofen is rapidly absorbed from the gastrointestinal tract with a bioavailability of 80-90%. Peak serum concentrations occur one to two hours after administration. If administered with food, peak serum concentrations are lower and achieved more slowly than when taken on an empty stomach. Food does not affect markedly total bioavailability.

Distribution

Ibuprofen is extensively bound to plasma proteins (99%). Ibuprofen has a small volume of distribution being about 0.12-0.2 L/kg in adults.

Biotransformation

Ibuprofen is rapidly metabolized in the liver through cytochrome P450, preferentially CYP2C9, to two primary inactive metabolites, 2-hydroxyibuprofen and 3-carboxyibuprofen. Following oral ingestion of the drug, slightly less than 90% of an oral dose of ibuprofen can be accounted for in the urine as oxidative metabolites and their glucuronic conjugates. Very little ibuprofen is excreted unchanged in the urine.

Elimination

Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours. The excretion of ibuprofen is virtually complete 24 hours after the last dose.

Special populations

Elderly

Given that no renal impairment exists, there are only small, clinically insignificant differences in the pharmacokinetic profile and urinary excretion between young and elderly.

Children

The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5 mg/kg to 10 mg/kg bodyweight) in children aged 1 year or over, appears similar to that in adults.

Children 3 months to 2.5 years appeared to have a higher volume of distribution (L/kg) and clearance (L/kg/h) of ibuprofen than did children >2.5 to 12 years of age.

Renal impairment

For patients with mild renal impairment increased unbound (S)-ibuprofen, higher AUC values for (S)ibuprofen and increased enantiomeric AUC (S/R) ratios as compared with healthy controls have been reported.

In end-stage renal disease patients receiving dialysis the mean free fraction of ibuprofen was about 3% compared with 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 4.2, 4.3 and 4.4).

Hepatic impairment

Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters.

In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) treated with racemic ibuprofen an average 2-fold prolongation of the half-life was observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of (R)-ibuprofen to the active (S)-enantiomer (see sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

There are no preclinical data of relevance for the safety assessment, apart from what has already been taken into account in this summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose, microcrystalline
Croscarmellose sodium
Hypromellose
Stearic acid
Silica, colloidal anhydrous
Magnesium stearate

Coating for <Product name> 400 mg film-coated tablet:

Hypromellose
Macrogol
Talc
Titanium dioxide (E171)

Coating for <Product name> 600 mg film-coated tablet:

Hypromellose
Macrogol
Talc
Titanium dioxide (E171)

Coating for <Product name> 800 mg film-coated tablet:

Hypromellose
Macrogol
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

<Product name> 400 mg: 3 years

<Product name> 600 mg: 3 years

<Product name> 800 mg: 2 years

6.4 Special precautions for storage

Store below 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

The tablets are packed into PVC/Alu blisters.

Pack sizes:

<Product name> 400 mg: 10, 12, 20, 24, 30, 36, 40, 48, 50, 100, 250 film-coated tablets

<Product name> 600 mg: 10, 20, 30, 40, 50, 100, 250 film-coated tablets

<Product name> 800 mg: 10, 20, 30, 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

4-April-2025