SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
IBU-FORT 200 mg/5 ml suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 ml suspension contains;

Active substance:

Ibuprofen	200 mg

Excipients:

Sorbitol (70%) (E420)	250 mg
Sucrose	1.875 g
Sodium benzoate (E211)	5 mg
Maltitol (E965)	500.0 mg
Polyoxyl 40 castor oil (PEG 40)	125 mg
Carmelose sodium	8.3-13.8 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Suspension
Almost white colored, characteristic odor (strawberry) suspension

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
It is indicated for the treatment of symptoms and signs of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. It is also used for the treatment of acute gout arthritis, acute musculoskeletal pain, postoperative pain, dysmenorrhea and fever reduction.

4.2. Posology and method of administration
Posology/frequency of administration and duration:
Absorption of the IBU-FORT accelerates when taken on an empty stomach, but it is recommended to apply it after meals, preferably in order to minimize gastrointestinal side effects.

Adults:
The average dose for mild to moderate pain is 1200 mg.

The daily dose is 200 mg to 400 mg per 4-6 hours depending on the condition of the patient.

Undesirable effects can be minimized by using the lowest effective dose required to control symptoms as soon as possible (see Section 4.4).

Route of administration:
Only for oral administration.

Ensure that the bottle is shaken well before use.

Additional information on special populations
Renal/Hepatic/Cardiac failure:
Caution should be exercised in patients with kidney, liver or hearth failure, because the use of NSAIDs such as ibuprofen can lead to impairment in renal functions. In these patients, the dose should be kept as low as possible and renal function should be monitored.

Pediatric population:
It is not recommended for use under 6 years.

Pediatric use (6-12 ages):

- For pain and fever 5-10 mg/kg/dose as 3-4 divided doses

Age	Weight (Average weight)	Ibuprofen Dose (minimum-maximum)	Measure (minimum-maximum)
6	18-22 kg (20 kg)	100 mg - 200 mg	2,5 ml - 5 ml
7-10	22-26 kg (24 kg)	120 mg - 240 mg	3 ml - 6 ml
11-12	30-34 kg (32 kg)	160 mg - 320 mg	4 ml - 8 ml

- For juvenile arthritis 30-40 mg/kg/day as 3-4 divided doses

Geriatric population:
The frequency of undesirable effects such as gastrointestinal (Gİ) bleeding and perforation that may be fatal with use of NDAIDs in this patient group is increased.

Thus, if NSAIDs needs to use for elderly patients, the possible smallest effective dose and the shortest duration of treatment should be preferred.

4.3. Contraindications

- Hypersensitivity to ibuprofen or any of the excipients in the product,
- Patients who have previously showed allergic reactions such as asthma, urticaria against aspirin or other NSAIDs,
- Patients with active or history of ulcerative colitis, Crohn's disease, recurrent peptic ulcer or gastrointestinal hemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding),
- Patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy,
- Patients with bleeding tendency,
- Patients with severe cardiac failure,
- Patients with severe hepatic failure,
- Patients with severe renal failure (Glomerular filtration < 30 ml/min),
- Patients in the period of pre or post-coronary artery bypass surgery,

- Last trimester of pregnancy.

4.4. Special warnings and precautions for use

Cardiovascular (CV) Risk
- NSAIDs may cause increased risk of cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

- İBU-FORT, is contraindicated for treatment of pain prior to coronary artery by-pass surgery.

Gastrointestinal (GI) risks
NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration and perforation of the stomach or intestines, which can be fatal. These adverse events can occur at any time with or without prior warning symptoms. Elderly patients are at a greater risk for serious gastrointestinal events.

To minimize the undesired effects, the lowest effective dose for management of the symptoms should be used for the shortest possible duration (see section 4.2 and below-mentioned gastrointestinal and cardiovascular risks).

İBU-FORT should be used with caution in patients with bronchial asthma or preexisting bronchial asthma, since it has been reported that ibuprofen causes bronchospasm in such patients.

İBU-FORT should be given with care to patients with a history of peptic ulceration and other gastrointestinal diseases, as these conditions may be exacerbated.

Caution is also required in patients with renal, hepatic or cardiac impairment since use of NSAIDs may result in deterioration of renal function. Dose levels should be kept as low as possible and renal function should be monitored in such patients.

Caution is required when administering İBU-FORT in patients with a history of heart failure or hypertension as edema cases associated with ibuprofen therapy have been reported.

As with the other NSAIDs, İBU-FORT may mask the symptoms of infection.

Cardiovascular and cerebrovascular effects

Patients with a history of hypertension and / or mild to moderate congestive heart failure should be monitored appropriately and recommendations should be made about their condition as edema and liquid retention cases associated with NSAIDs have been reported.

Cardiovascular effects

Cardiovascular Thrombotic Events:
Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with cardiovascular disease or risk factors for cardiovascular disease may be

at greater risk. To minimize the potential risk for an adverse cardiovascular event in patients treated with NSAIDs, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular events and the steps to take if such events occur.

There is no consistent evidence that concurrent use of aspirin mitigates the risk of serious cardiovascular thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID increase the risk of serious GI events.

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following coronary artery bypass surgery found an increased incidence of myocardial infarction and stroke.

Hypertension:

NSAIDs including IBU-FORT, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking thiazides, or loop diuretics may have impaired response to these therapies when taking NSAIDs.

NSAIDs, including IBU-FORT, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema:
Fluid retention and edema have been observed in some patients taking NSAIDs. IBU-FORT should be used with caution in patients with fluid retention or heart failure.

Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

<u>Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation</u>
NSAIDs, including IBU-FORT, can cause serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper gastrointestinal adverse event on NSAID therapy, is symptomatic. Upper gastrointestinal ulcers, bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious gastrointestinal event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a gastrointestinal bleed compared to patients treated with neither of these risk factors. Other factors that increase the risk of gastrointestinal bleeding in patients treated with NSAIDs

include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal gastrointestinal events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse gastrointestinal event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of gastrointestinal ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal event is suspected. NSAID therapy should be even discontinued until a serious gastrointestinal adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing ibuprofen doses, in patients with a history of ulcer (particularly if complicated with hemorrhage or perforation) 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.

Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) in the initial stages of treatment.

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

The elderly have an increased frequency of adverse reactions to NSAIDs (especially gastrointestinal bleeding and perforation which may be fatal).

Renal Effects

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration.

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathological changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandins formation and, secondarily, in renal blood flow, which may accelerate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those who are taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID therapy usually results in recovery to the pre-treatment state.

Advanced Renal Failure

No information is available from controlled clinical studies regarding the use of IBU-FORT in patients with advanced renal disease. Therefore, treatment with IBU-FORT is not recommended in these patients with advanced renal disease. If IBU-FORT therapy must be initiated, close monitoring of the patients renal function is advisable.

Anaphylactic Reactions

As it is for other NSAIDs, anaphylactoid reactions may occur in patients who were not known to be exposed to IBU-FORT previously. IBU-FORT should not be given to patients with Aspirin triade. This symptom complex typically develops in asthma patients having rhinitis with or without nasal polyp or in patients showing potential fatal, serious bronchospasm after taking aspirin or other NSAIDs.

Ocular Effects

In trials, no ocular changes that would be caused by ibuprofen administration were shown. In rare cases, undesired ocular disorders as papillitis, retrobulber optical neuritis and papilledema were reported by patients using NSAIDs including Ibuprofen, but the relation with cause and effect could not be established; thus ophthalmologic examination should be made in patients developing eye disorder during ibuprofen treatment.

Hematological effects

As it is for other NSAIDs, ibuprofen can inhibit the platelet aggregation and prolong the bleeding time.

Pre-existing Asthma

Patients with asthma may have asthma sensitive to aspirin. In patients having asthma sensitive to aspirin, usage of aspirin is associated with severe bronchospasm which may be fatal. In such patients sensitive to aspirin, as cross reactions were reported among aspirin and other NSAIDs including bronchospasm, IBU-FORT should not be used and it should be used with caution for patients having pre-existing asthma.

Aseptic Meningitis

Aseptic meningitis has been observed on rare occasions in patients with ibuprofen therapy. Although it is probably more likely to occur in patients with systematic lupus erythematous and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Dermatological Effects

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs. Patients appear to be at the highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Since it contains sorbitol (70%) (E420), patients with rare hereditary problems of fructose intolerance should not take this medicine.

Each one dose (5 ml) contains 1875 g sucrose. This should be considered in patients with diabetes.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not take this medicine.

IBU-FORT contains less than 1 mmol (23 mg) of sodium per dose (5 ml); i.e. it is "sodium free".

Since it contains maltitol (E965), patients with rare hereditary problems of fructose intolerance should not take this medicine.

Polyoxyl 40 castor oil (PEG 40) contained in the content of IBU-FORT may cause nausea and diarrhea.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised in patients being treated with any of the following drugs as interaction has been reported in some patients:

Alcohol: Concomitant take of ibuprofen and alcohol should be avoided as it may increase the risk of important gastrointestinal side effects such as bleeding.

Aminoglycosides: NSAIDs may reduce the excretion of aminoglycosides .

Antihypertensives (such as Angiotensin converting enzyme (ACE) inhibitors): Decrease in antihypertensive effect.

Anticoagulants (e.g. warfarin): The effects of warfarin and NSAIDs on gastrointestinal bleeding are synergistic. e.g. increase in anticoagulant effect.

Antithrombotic agents and selective serotonin reuptake inhibitors (SSRI): Increased risk of gastrointestinal bleeding with NSAIDs.

Aspirin (Acetylsalicylic acid): As with the other medicinal products containing an NSAID, the combination of acetylsalicylic acid and other NSAIDs should be avoided due to the increased potential for adverse effects. Experimental data suggest that Ibuprofen may inhibit the effect of low dose aspirin 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.)

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

Diuretics: Clinical trials and post marketing observations have shown that IBU-FORT reduces the natriuretic effect of certain diuretics such as furosemide and thiazide. This effect has been associated with the inhibition of renal prostaglandin synthesis. During concurrent therapy with NSAIDs, patients should be carefully monitored for signs of renal insufficiency and be assured that diuretic activity persists.

Cardiac glycosides: NSAIDs can exacerbate heart failure, reduce glomerular filtration and increase plasma cardiac glycoside levels.

Captopril: Experimental studies indicate that ibuprofen counteracts the effect of captopril on increased sodium excretion.

Quinolone derivative antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolone may

have increased risk of developing convulsions. The interaction studies have been conducted only in adults.

Cox-2 inhibitors and other NSAIDs: use with other NSAIDs including selective cyclooxygenase-2 selective inhibitors should be avoided due to potential additive effects.

Cholestyramine: The concomitant administration of ibuprofen and cholestyramine can reduce the absorption of ibuprofen from gastrointestinal tract.

Corticosteroids: May increase the risk of gastrointestinal ulceration or bleeding, when co-administered with the NSAIDs.

Lithium: NSAIDs increased plasma lithium levels (15%) and reduced renal lithium clearance (%20). This effect has been associated with the inhibition of renal prostaglandin synthesis. Thus, patients should be carefully monitored for lithium toxicity when NSAIDs and lithium are used concomitantly.

Methotrexate: NSAIDs have been reported to reduce methotrexate accumulation in rabbit kidney sections. This may indicate that NSAIDs may increase methotrexate toxicity. Caution is required when administering concomitantly of methotrexate and NSAIDs.

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

Cyclosporine: It is presumed that administering of NSAIDs concomitantly with cyclosporine may increase the risk of nephrotoxicity because of decreased prostacyclin synthesis in kidney. Therefore in case of combination treatment renal function must be closely monitored.

Selective serotonin reuptake inhibitors, SSRIs (e.g. paroxetine, fluoxetine, sertraline): SSRI and NSAID each involve an increased risk of bleeding e.g. from the gastrointestinal tract. This risk increases at concomitant treatment. The mechanism may be associated with a decreased uptake of serotonin in the thrombocytes (see section 4.4).

Sulphonylureas: NSAIDs may potentiate the effects of sulphonylurea medications. There are rare reports of hypoglycaemia in patients on sulphonylurea medications receiving ibuprofen.

Other analgesics: Concomitant use of two or more NSAIDs should be avoided.

Tacrolimus: When NSAIDs are co-administered with tacrolimus, possible increased risk of nephrotoxicity may be expected. It is presumed that administering of NSAIDs concomitantly with tacrolimus may increase the risk of nephrotoxicity because of decreased prostacyclin synthesis in kidney. Therefore, in case of combination treatment renal function must be closely monitored.

Ticlopidine: NSAID-products should not be combined with ticlopidine because of inhibition of platelet function.

Zidovudine: There may be an increased risk of hematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of hematoma and hemarthroses in HIV(+) hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

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, particularly when high-dose ibuprofen is administered concomitantly with potent CYP2C9 inhibitors such as voriconazole or fluconazole.

Additional information on special populations:
Interaction studies of special populations were not conducted.

Pediatric population:
Interaction studies of special populations were not conducted.

4.6. Pregnancy and lactation
General recommendation
Pregnancy category is C (D at the 3rd trimester).

Women with Childbearing Potential/Birth control (Contraception)
If ibuprofen would be used by a woman attempting to conceive, or during the first and second trimesters of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal 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/fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimesters of pregnancy, IBU-FORT should not be given unless clearly necessary. If IBU-FORT is used by a woman attempting to conceive, or during the first and second trimesters of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension),
- renal dysfunction, which may progress to renal failure with oligohydramnios

the mother and the neonate, at the end of pregnancy, to:

- prolongation of bleeding time
- inhibition of uterine contractions resulting in delayed or prolonged labor

Consequently, IBU-FORT is contraindicated during the third trimester of pregnancy.

Lactation

In limited clinical studies, like all NSAIDs, ibuprofen appears in the breast milk in very low concentrations. Therefore, use of IBU-FORT is not recommended in lactating women whenever possible.

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

İBU-FORT may cause undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances. If such undesirable effects occur, patients should be warned not to drive or use machines.

4.8. Undesirable effects

The mode of occurrence of adverse events reported for oral ibuprofen, are qualitatively similar to those reported with other NSAIDs.

Undesirable effects that are at least likely to be associated with ibuprofen have been demonstrated by MedDRA frequency convention and the system organ class according to the following 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 available data).

System Organ Class	Frequency	Undesirable effect
Infections and infestations	Uncommon	Rhinitis
	Rare	Aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematous and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation
Blood and lymphatic system disorders	Uncommon	Leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia and hemolytic anemia
Immune system disorders	Rare	Anaphylactic reaction
Psychiatric diseases	Uncommon	Insomnia, anxiety
	Rare	Depression, confusional status hallucination
Nervous system diseases	Common	Headache, dizziness
	Uncommon	Paresthesia, somnolence
	Rare	Optic neuritis
Eye disorders	Uncommon	Blurred vision

	Rare	Toxic optic neuropathy
Ear and Labyrinth disorders	Uncommon	Hearing impaired
	Rare	Tinnitus, vertigo
Respiratory, thoracic and mediastinal disorders	Uncommon	Asthma, bronchospasm, dyspnea
Gastrointestinal disorders	Common	Dyspepsia, diarrhea, nausea, vomiting, abdominal pain, flatulence, constipation, melena, hematemesis, gastrointestinal hemorrhage
	Uncommon	Gastritis, duodenal ulcer, gastric ulcer, oral ulceration, gastrointestinal perforation
	Very rare	Pancreatitis
	Unknown	Colitis and Crohn's disease
Hepato-biliary disorders	Uncommon	Hepatitis, jaundice, hepatic dysfunction
	Rare	Hepatic damage
	Very rare	Hepatic impairment
Skin and subcutaneous tissue disorders	Common	Skin rash
	Uncommon	Urticaria, pruritus, purpura, angioedema, photosensitivity
	Very rare	bullous skin inflammation including Stevens-Johnson's syndrome, toxic epidermal necrolysis and erythema multiform
	Unknown	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)
Renal and urinary disorder	Uncommon	Tubule interstitial nephritis, nephrotic syndrome and renal impairment
General disorders and administration site conditions	Common	Fatigue
	Rare	Edema

Edema, hypertension and heart failure have been reported in association with non-steroidal anti-inflammatory therapy. Clinical trial data and epidemiological data suggest that use of ibuprofen, particularly at a high dose 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).

The most common adverse effects are seen with the GI system. Particularly in the elderly, ulcers, perforation or bleeding may be sometimes fatal. Following ibuprofen administration, nausea, vomiting, diarrhea, indigestion, constipation, dyspepsia, abdominal pain, melena, hematemesis,

hypertension and heart failure as well as ulcerative stomatitis, exacerbation of and Crohn's disease have been reported. Less frequently, gastritis was seen.

In the majority of cases where aseptic meningitis has been reported, there has been some form of underlying autoimmune disease (in particular, systemic lupus erythematosus and related connective tissue diseases).

Immune system disorders: Following therapy with NSAIDs, hypersensitivity reactions have been reported. These were consisting of non-specific allergic reactions and anaphylaxis, respiratory tract reactivity such as asthma, aggravated asthma, bronchospasm and dyspnea or skin disorders including rash (various types), pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiform).

Exceptionally, occurrence of serious skin and connective tissue infectious complications has been reported in connection with varicella.

Ibuprofen can inhibit reversible platelet aggregation, resulting in prolongation of bleeding time.

4.9. Overdose

Toxicity

There is risk of symptoms occurring at doses above 80–100 mg/kg. At doses above 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 resulted in severe intoxication, 3.2 g in a 6-year-old mild to moderate intoxication, 2.8–4 g in a 1,5 year-old and 6 g in a 6-year-old severe intoxication, 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 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. Hypernatremia, kidney effects, hematuria. Possibly liver effects. Hypothermia. Adult respiratory distress syndrome has rarely been reported. Metabolic acidosis may occur in severe intoxications.

Treatment

If warranted, gastric lavage, carbon. In the event of gastrointestinal problems, antacids are administered. In the event of hypotension, intravenous fluid and, if required, inotropic support. Ensure adequate diuresis. Correction of acid-base and electrolyte disorders. Frequent and prolonged convulsions must be treated with intravenous diazepam. Other symptomatic therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory drugs
ATC Code: M01AE01

5.1. Pharmacodynamic Properties

Ibuprofen is a propionic acid derivative having analgesic anti-inflammatory and antipyretic effects. Therapeutic effects of ibuprofen are thought to occur as a result of its non-selective

inhibitory effect on cyclooxygenase enzyme. Due to this inhibitory effect, ibuprofen leads to a significant decrease in prostaglandin synthesis.

Experimental data suggest that ibuprofen may inhibit the effect of low-dose aspirin on platelet aggregation when they are administered concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release aspirin administration (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding the extrapolation of ex vivo data to the clinical situation suggest that no firm conclusions can be drawn for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2. Pharmacokinetic Properties

General 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. Peak plasma concentrations are reduced and time to reach these levels is slower when ibuprofen is taken with food compared to when taken on an empty stomach. Food does not affect the total bioavailability to a relevant extent.

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 with cytochrome P450, preferably CYP2C9 to two primary inactivated metabolites as 2-hydroxybiprofene and 3-carboxyibuprofen in the liver. Following oral ingestion, a dose of slightly less than 90% of the oral dose of ibuprofen appears in the form of oxidative metabolites and their glucuronic conjugates in urine. A small amount of 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.

Linearity/Non-linearity

The pharmacokinetics of ibuprofen are linear.

Characteristics in patients

Renal impairment:

For patients with mild renal impairment increased unbound (S)-ibuprofen, higher area under the Curve (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 hemodialysis (see sections 4.2, 4.3 and 4.4).

Hepatic impairment:
Alcoholic liver disease with 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).

Elderly:
In cases without renal insufficiency, in pharmacokinetic profile and urinary excretion, only minor, clinically insignificant changes are observed between young and elderly patients.

Children:
The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5 mg/kg to 10 mg/kg body weight) in children aged one 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.

5.3. Preclinical safety data
Acute toxicity:

Species	Sex	Dosing range mg/kg	Max. Ineffective level mg/kg	Min. Dose with apparent effect mg/kg	Max. non-lethal dose mg/kg	Min. lethal dose mg/kg	Max. Non-fetal dose mg/kg
Mouse (oral)	M	200-1600	200	400	200	400	800
Mouse (ip)	M	100-1600	100	200	100	200	800
Rat (oral)	M	400-1600	400	800	800	1600	1600
Rat (sc)	M	400-1600	800	1600	800	1600	1600

Chronic toxicity:
Gastrointestinal tract ulceration was the only constant pathological finding, which were seen with the following lowest daily doses: 300 mg/kg in mice; 180 mg/kg in rats; 100 mg/kg in monkeys; 8 mg/kg in dogs. No gastrointestinal damage level was 60 mg/kg a day for 6 months in rats and 75 mg/kg a day for 90 days in mice. In a study, renal papillary changes were found in rats at the end of two-years. These findings are typical for non-steroidal anti-inflammatory drugs and relevance of these to humans is in question.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Xanthan gum
Hydroxypropyl methyl cellulose
Glycerin
Sorbitol (70%) (E420)
Maltitol (E965)
Sodium benzoate (E211)
Sucrose
Polyoxyl 40 castor oil (PEG 40)
Citric acid
Strawberry flavor
Ammonium glycyrrhizate
Microcrystalline cellulose and carmellose sodium
Masking flavor
Deionized water

6.2. Incompatibilities

There is no evidence for any existing incompatibilities of IBU-FORT with any drug or agent.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at room temperature below 25ºC.

6.5. Nature and contents of container

IBU-FORT is marketed in amber colored glass bottles (Type III) closed with pilfer-proof high density polyethylene (HDPE) cap and low density polyethylene seal

Each carton box includes; 1 bottle containing 30 ml or 100 ml suspension, and 1 plastic pipette of 5 ml graduated with 0.5 ml.

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with "Directive on Control of Medical Waste" and "Directive on the Control of Packaging and Packaging Waste".

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

253/40

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 20.09.2013

Date of latest renewal: 29.11.2018

10. DATE OF REVISION OF THE TEXT

01.10.2019