SPEDIFEN®

400 mg Granules

Ibuprofen (as L-arginine salt)

Product Description: Sachets contain white granules with a characteristic apricot odour.

Pharmacodynamics and Pharmacokinetics
ATC code: M01AE01
Pharmacotherapeutic group: non-steroidal anti-inflammatory/antirheumatic drugs.
SPEDIFEN contains the active substance ibuprofen in the form of arginate salt. Ibuprofen is an anti-inflammatory drug with analgesic, antipyretic and anti-rheumatic activities. Its effect comes mainly from an inhibition of the synthesis of prostaglandins that play a role in inflammatory and painful process.
The ibuprofen arginate has the same pharmacological effect of ibuprofen, but is characterized by a better solubility. The effect begins approximately within 30 minutes.
Absorption
Granulate: The maximum concentration of active compound of 57 mcg / ml on average ibuprofen is reached in serum 17-24 minutes after oral administration of 400 mg ibuprofen (as ibuprofen arginate) respectively.
If the administration of SPEDIFEN occurs after meals, absorption is slower and the maximum serum concentrations are lower.
Distribution
The serum half-life of 1.5-2 hours. Binding to albumin approx. 99%.
Metabolism
After hepatic metabolism, ibuprofen is rapidly eliminated, mainly in the form of pharmacologically inactive metabolites, mainly by the kidneys.
Elimination
An ibuprofen accumulation does not occur even during a long-term therapy, ibuprofen, and these metabolites are almost completely removed 24 hours after the last dose.

Indication
Pain: headache including migraine, toothache, dysmenorrhoea, neuralgia, osteoarticular and muscular pain, episiotomy and post- partum pain, pain following tooth extraction, post-operative pain, soft tissues injuries and traumatisms.
Rheumatic Inflammatory diseases: rheumatoid arthritis, ankylosing spondylitis, Still`s Disease. Degenerative rheumatic disease: osteoarthritis (cervical, dorsal and lumbar arthritis, gonarthritis, coxarthritis, polyarthritis, etc)
Non-articular rheumatic conditions: tendonitis, fibrositis, bursitis, myalgia, lumbago, scapolohumeral periarthritis, sciatica, radiculoneuritis.

Recommended Dose
Adults: 400 mg sachets: 2-4/day according to medical advice. The maximum daily dose should not exceed 1600mg
The administration of the first daily dose on awakening (with food) patients can be advantageous to provide relief of the morning stiffness associated with arthritis. The following daily doses should be taken during or after meals. In elderly the posology must be carefully assessed by the physician since a reduction of the above mentioned dosage may be needed.
The content of each sachet must be dissolved in a glass of water (50-100 ml) and immediately taken.

Mode of Administration
Oral

Contraindications
- Hypersensitivity to the active substance or to any of the excipients according to the composition.
- History of bronchospasm, urticaria, or allergic symptoms or any similar event after taking acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Gastric and/ or duodenal or active gastrointestinal bleeding.
- Inflammatory bowel disease (Crohn's disease, ulcerative colitis).
- Cerebrovascular hemorrhage.
- Hemorrhagic diathesis.
- Third trimester of pregnancy
- Severe disturbances of liver function (liver cirrhosis and ascites).
- Severe renal impairment (creatinine clearance < 30ml/ min).
- Severe heart failure (NYHA III-IV).
- Treatment of postoperative pain after heart bypass surgery (or after using a heart-lung machine).

Warnings and Precautions
General warning for the use of systemic nonsteroidal anti-inflammartory drugs (NSAIDs) Gastrointestinal effects: Ulcers and gastrointestinal bleeding or perforation can be observed in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs), selective COX-2 or not. These side effects may occur at any time, without warning or known history. To reduce this risk, it is appropriate to administer the lowest effective dose for a treatment duration as short as possible.
Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding). When GI bleeding or ulceration occurs, the treatment should be stopped. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti- platelet agents such as aspirin.
Cardiovascular and cerebrovascular effects: Placebo controlled studies have shown some selective COX-2 increased risk of cardiovascular and cerebrovascular thrombotic complications. But it is unclear at present whether this risk is directly correlated with selective COX-1/ COX-2 NSAIDs.
Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/ day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200mg/ day) is associated with an increased risk of arterial thrombotic events. Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400mg/ day) should be avoided. Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.
Cases of Kounis syndrome have been reported in patients treated with ibuprofen. Kounis syndrome was defined as cardiovascular symptoms secondary to an allergic reaction or hypersensitivity associated with constriction of coronary arteries and which may induce myocardial infarction.
Renal effects: the effects of nonsteroidal anti-inflammatory drugs on the kidney include fluid retention with oedema and / or hypertension. In patients with impaired cardiac function and other conditions predisposing to fluid retention, ibuprofen should be used with caution. Patients with severe dehydration or postoperative changes in blood volume should be rehydrated before starting ibuprofen treatment and then closely monitored. There is a risk of kidney function disorder, especially in dehydrated children and adolescents.
During long-term treatment, as with other nonsteroidal anti-rheumatic drugs, renal papillary necrosis and other renal diseases may occur. Renal toxicity has also been observed in patients in whom renal prostaglandins play a compensatory role in renal perfusion. In these patients, administration of nonsteroidal anti- rheumatic drugs may inhibit prostaglandin synthesis in the kidneys depending on the dose administered, decrease renal blood flow and cause obvious renal decompensation. These reactions occur mainly in patients with impaired hepatic function, renal function or cardiac function, when concomitant use of diuretics or ACE inhibitors (angiotensin converting enzyme) and in elderly patients.
Elderly patients: In elderly patients, there is an increased incidence of adverse events after taking NSAIDs, especially bleeding and gastrointestinal perforation, also with a life- threatening outcome.
Respiratory disorders: In patients suffering from or having suffered from bronchial asthma, chronic rhinitis or allergic disease, ibuprofen may cause bronchial spasm, urticaria or angioedema.
Aseptic meningitis: in patients who have developed lupus erythematosus or collagenosis due to an increased risk of aseptic meningitis. *Other NSAIDs*: The use of ibuprofen in combination with NSAIDs, including selective cyclooxygenase-2 inhibitors, should be avoided.
Severe skin reactions
Severe skin reactions, including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome) and drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) and cases of acute generalized exanthematous pustulosis (AGEP), which may be life-threatening or fatal, have been reported in association with ibuprofen use (see "Side Effects"). The majority of these reactions occurred within the first month of treatment. If signs and symptoms indicative of these reactions appear, ibuprofen should be immediately discontinued and alternative treatment should be considered (as appropriate).
Masking of symptoms of underlying infections
Ibuprofen may mask symptoms of infection, which might delay the start of adequate treatment and, therefore, worsen the outcome of the infection. This has been observed in community-acquired bacterial pneumonia and bacterial complications of chickenpox. In isolated cases, in temporal association with the use of NSAIDs, a worsening of infectious inflammations (e.g. development of necrotising fasciitis) has been described. When ibuprofen is administered to relieve fever or pain related to infection, the infection should be monitored. In non-hospital settings, the patient should seek medical attention if symptoms persist or worsen.
Visual Disorders: Patients with visual disturbances during ibuprofen therapy should discontinue treatment and undergo ophthalmologic examination.
Liver function test: NSAIDs may cause increased liver function test results.
Risk of GI Ulceration, Bleeding and Perforation with NSAID
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.
Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

Instruction for use/handing
The medicinal product has to be suspended in water before oral administration.

Interactions with Other Medicaments
Other nonsteroidal anti-inflammatory and/ or glucocorticoid as well as alcohol: Intensification gastrointestinal side effects, increased risk of gastrointestinal bleeding.
Salicylic acid removes ibuprofen from its protein binding. When used concomitantly, caution is advised because of the increased risk of gastrointestinal adverse effects.
Acetylsalicylic acid (low dose): Experimental evidence suggests that ibuprofen can competitively inhibit the antiplatelet effect of a concomitant low dose of acetylsalicylic acid. However, data are limited and extrapolation of ex vivo data to the uncertain clinical situation. Therefore, with respect to regular ibuprofen, it is not possible to draw definitive conclusions; a clinically significant effect seems unlikely when taking ibuprofen occasionally (see "Properties/Effects").
Probenecid, sulfinpyrazone: Ibuprofen is eliminated more slowly; the uricosuric action of probenecid and sulfinpyrazone is reduced.
Oral anticoagulants: Nonsteroidal anti- inflammatory drugs may enhance the effect of anticoagulants such as warfarin.

Zambon 1906 — Property of Zambon S.p.A, Via Lillo del Duca 10, 20091 Bresso / Milano		PRODOTTO / BRAND: **IS SPEDIFEN 400MG BST MY**	LATO STAMPA BIANCA/VOLTA (SIDE PRINT FRONT/REAR): **LATO BIANCA / FRONT SIDE**
		REV MOCKUP APPROVATO - DATA: **N/A**	ARTWORK REV: **3**
CODICE / ITEM: **H02V603**	ED. / VERSION N.: **E04.1124**	DATA / DATE: **22/11/2024**	CONFORME AL MASTER LAYOUT - NOTE: **FI 512 CC**
DIMENSIONI / SIZE: **135x420**	FORM./TECH.CODE/MASTER LAYOUT: **FI 512 CC**	COLORI / COLORS NO: **2**	BRAILLE: **N/A**
COD. CLIENTE / CUSTOMER CODE: **N/A**	PHARMA CODE: **223 (XXIIIII)**	EDGE CODE: **N/A**	BLACK; P 390 U
STABILIMENTO / PLANT: **CADEMPINO**	PACKAGING LINE: **N/A**		FONT/CORPO MIN./INTERLINEA (FONT/MIN. SIZE/SPACING): **HELVETICA NEUE Corpo 8 pt. - Interlinea 8 pt.**
CHANGE DESCRIPTION: **DOSSIER 126_2024 MODIFICA TEST/EDIT TEXT**			ISTRUZIONI FORNITORE / SUPPLIER INSTRUCTION: **N/A**

Scale 1:1

Inhibitors of platelet aggregation inhibitors and selective serotonin reuptake: Increased risk of gastrointestinal bleeding.
Antidiabetics: Ibuprofen enhances the hypoglycemic effect of oral antidiabetic agents and insulin. It may be necessary to adjust the dose.
Aminoglycosides: Non-steroidal anti- inflammatory drugs may limit the elimination of aminoglycosides.
Diuretics: The effectiveness of furosemide and thiazide diuretics may be decreased, probably because of sodium retention, which is based on inhibition of prostaglandin synthesis in the kidneys.
Anti-hypertensives: a decrease in the effectiveness of anti-hypertensives is to be expected. Therefore, simultaneous treatment with NSAIDs and ACE inhibitors or a beta- blocker may increase the risk of acute renal failure.
Histamine H2 receptor antagonists: There is no evidence that ibuprofen has a clinically important interaction with cimetidine or ranitidine.
Digoxin: plasma concentrations of digoxin may be increased.
Phenytoin: The plasma concentration of phenytoin may be increased.
Lithium: the plasma concentration of lithium can be increased.
Methotrexate: Increased toxicity of methotrexate.
Zidovudine: Concomitant use of zidovudine and ibuprofen increases the risk of haemarthritis and haematomas in HIV (+) hemophiliac patients.
Tacrolimus: Concomitant use of tacrolimus and ibuprofen may increase the risk of nephrotoxicity.
Voriconazole or fluconazole: Concomitant intake of voriconazole, fluconazole and ibuprofen may lead to an increase in ibuprofen exposure and plasma concentration of ibuprofen.
Mifepristone: Concomitant use of NSAIDs may lead to increased exposure to NSAIDs.
Theoretically, a decrease in the efficacy of mifepristone can occur because of the anti- prostaglandin properties of NSAIDs. Studies suggest that concomitant administration of ibuprofen on the day of administration of prostaglandins (or when necessary) does not adversely affect the effect of mifepristone or the clinical efficacy of a discontinuation of pregnancy.
Baclofen: increased toxicity of baclofen. *Quinolones:* concomitant use of NSAIDs may lead to an increased risk of seizures.
Cyclosporine: The toxic effect on the kidneys may be increased.
Plant extracts: Ginkgo biloba may increase the risk of bleeding associated with non-steroidal anti-inflammatory drugs.
Interactions with diagnostic tests:
- Bleeding time (may prolong bleeding time up to 1 day after discontinuation of treatment).
- Concentrations of glucose in the serum (can be decreased).
- Lightening creatinine (may be decreased).
- Hematocrit or hemoglobin (may be decreased).
- BUN, serum creatinine and serum potassium (may be increased).
- Tests of liver function (elevation of transaminases)

Pregnancy and Lactation
Inhibition of prostaglandin synthesis may adversely affect the course of pregnancy and/ or the development of the embryo or fetus. Data from epidemiological studies, following the use of an inhibitor of prostaglandin synthesis in the first stage of pregnancy, suggest an increased risk of miscarriage, heart malformation and gastroschisis. This risk is believed to increase with the dose and duration of treatment.
In animals, administration of an inhibitor of prostaglandin synthesis leads to increased losses pre- and post-implantation and embryo-fetal mortality. In addition, increased incidences of various malformations, including cardiovascular, have been observed in animals given an inhibitor of prostaglandin synthesis during the period of organogenesis.
Unless clearly necessary, the use of ibuprofen should be avoided in the first and second trimester of pregnancy. When using ibuprofen in a woman attempting to conceive, or during the first or second trimester of pregnancy, the dose and duration of treatment should be kept as low as possible.
Oligohydramnios/Neonatal renal failure/Ductus arteriosus constriction
The use of NSAIDs in the 20th week of pregnancy or later may cause fetal renal dysfunction, leading to oligohydramnios and, in some cases, neonatal renal impairment. These undesirable effects are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID treatment initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. After market introduction, invasive procedures such as exchange transfusion or dialysis were required in some cases of impaired neonatal renal function.
In addition, ductus arteriosus constriction has been reported after the treatment in the second trimester, which resolved in most cases after discontinuation of treatment.
Consider ultrasound monitoring of amniotic fluid and fetal heart if the treatment with Spedifen extends beyond 48 hours.
Discontinue Spedifen if oligohydramnios or ductus arteriosus constriction occurs and perform a follow up examination according to clinical practice.
Ibuprofen is contraindicated during the third trimester of pregnancy. All inhibitors of prostaglandin synthesis can;
- expose the fetus to the following risks:
  - a cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension);
  - a renal dysfunction which may progress to renal failure associated with oligohydramnios.
- expose the mother and the newborn to the following risks:
  - a possible variation bleeding time due to aggregation inhibiting action which may occur even after administration of very low doses of medication;
  - an inhibition of uterine contractions resulting in terms of delays or prolonged labor.

Fertility: The use of ibuprofen may have a negative impact on female fertility and is therefore not recommended for women planning pregnancy. The cessation of ibuprofen
- based treatments should also be considered in women who fail to become pregnant or are undergoing fertility tests.
Lactation: The NSAIDs are excreted in human milk. As a precaution, SPEDIFEN therefore should not be administered to lactating women. If treatment is essential, it is then necessary to feed the baby with a biberon.

Side Effects
Frequency: Very common (≥1/10), common (<1/10, ≥1/100), uncommon (<1/100, ≥1/1000), rare (<1/1000, ≥1/10'000), very rare (<1/10'000), unknown (it cannot be defined on the basis of the available data).

System-organ class	Frequency
Haemolymphopoietic system disorders	
Haematological effects such as agranulocytosis, thrombocytopenia, neutropenia, aplastic anaemia, haemolytic anaemia.	Rare
Anemia	Unknown
Immune system disorders	
Allergic reaction	Uncommon
Lupus erythematosus syndrome, aseptic meningitis in patients suffering from autoimmune diseases such as lupus erythematosus, autoimmune hemolytic anemia, anaphylaxis.	Rare
Anaphylactic shock.	Unknown
Psychiatric disorders	
Depression, anxiety, confusional state.	Uncommon to common
Psychotic states	Very rare
Nervous system disorders	
Headache, dizziness	Common
Effects on the central nervous system such as limitation of the ability to react (in particular in interaction with alcohol), drowsiness.	Uncommon to common
Paresthesia	Rare
Eye disorders	
Vision disorders are normally reversible with discontinuation of treatment.	Uncommon to common
Toxic amblyopia, optic neuritis	Rare
Papilledema	Unknown
Ear and labyrinth disorders	
Ear disorder, Hypoacusis.	Uncommon to common
Heart disorders	
Heart failure, Kounis syndrome	Unknown
Vascular disorders	
Arterial thrombosis, hypertension, hypotension	Unknown
Respiratory, thoracic and mediastinal disorders	
Bronchospasm, asthma, aggravated asthma, dyspnea	Uncommon
Risk of acute pulmonary oedema in patients with heart failure	Rare
Throat irritation	Unknown
Gastrointestinal disorders	
Dyspepsia, diarrhoea	Very common
Gastrointestinal side effects such as nausea, abdominal fullness, heartburn, abdominal pain, anorexia, constipation, flatulence, vomiting, erosive gastritis, blood loss from the rectum (up to anaemia).	Common
Peptic ulcer, gastrointestinal hemorrhage, melena, gastritis	Uncommon
Ulceration or perforation of the gastrointestinal tract with hemorrhages, haematemesis, ulcerative stomatitis, aggravated colitis, aggravated Crohn's disease.	Rare
Hepatobiliary disorders	
Liver disorder, liver failure	Rare
Liver injury, hepatitis, jaundice	Unknown
Skin and subcutaneous tissue disorders	
Hypersensitivity reactions such as urticaria, purpura, itching, rash	Common
Angioedema	Uncommon
Bullous rashes, severe skin reactions (including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis), photosensitivity reaction.	Very rare
Aggravation of skin reactions, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis (AGEP).	Unknown
Kidney and urinary tract diseases	
Haematuria, renal papillary necrosis, interstitial nephritis, renal function disorders with oedema formation	Rare
Acute renal impairment	Very rare
Systemic disorders and conditions related to the site of administration	
Oedema	Unknown
Investigations	
Abnormal liver function test	Rare
Abnormal renal function test	Unknown

Symptoms and Treatment of Overdose
The small and frequent symptoms of overdose are nausea, vomiting, dizziness, somnolence and tremors. More rarely headache, tinnitus, ataxia, tachycardia, miosis, reversible elevation of transaminases and bilirubin, thrombocytopenia.
Prolonged use at doses higher than those recommended may cause severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalized weakness.
Serious symptoms are rare as loss of consciousness (coma), metabolic acidosis, cramps and acute renal failure; apnea in children < 2 years.
Severe symptoms are possible from 400 mg/ kg although doses of 60 g and even up to 100 g have been supported. Among the elderly, infants, liver and kidney disease and alcoholics, severe symptoms can already occur at lower doses.
From a dose > 200 mg/ kg (in young children) or 20 g (adults), detoxification using activated carbon (1 g/ kg body weight as a single administration in aqueous suspension orally) should be performed.
At an excessive overdose, gastric lavage followed by administration of activated charcoal within the next hour is recommended. Medical surveillance is required when doses >
300 mg/ kg or with high risk. Duration of monitoring: 4 hours, 12 hours for delayed preparations.
Laboratory analysis of transaminases, creatinine and bilirubin. In symptomatic patients, further analysis of blood gases, electrolytes and thrombocytes.

Storage Condition:
Store below 30°C

Shelf Life: 3 years

Pack size: 30 sachets per box

Manufacturer:
Zambon Switzerland Ltd, 6814 Cadempino, Switzerland

Date of Revision: October 2024

H02V603 E04.1124 FI512 CC cp.8/8

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CHANGE DESCRIPTION:
DOSSIER 126_2024
MODIFICA TEST/EDIT TEXT

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REV MOCKUP APPROVATO - DATA: **N/A**
ARTWORK REV: **3**
CONFORME AL MASTER LAYOUT - NOTE: **FI 512 CC**
COLORI / COLORS NO: **2**
BRAILLE: **N/A**
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HELVETICA NEUE
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ISTRUZIONI FORNITORE / SUPPLIER INSTRUCTION:
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Scale 1:1