Spedifen®
Ibuprofen
Film-coated tablet

Cardiovascular Risk
- NSAIDs may cause an increased risk of serious 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
- NSAIDs is contraindicated for the treatment of perioperative pain in the setting of coronaryartery bypass graft (CABG) surgery

Gastrointestinal Risk
- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomatch or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

COMPOSITIONS
SPEDIFEN 400 mg film-coated tablet, each tablet contains 400 mg Ibuprofen as L-arginine salt.
SPEDIFEN 400 mg film-coated tablet also contains : Sodium hydrogen carbonat, cropovidone, magnesium stearate, Hypermellose, sucrose, Titanium dioxide and Macrogol 4000.

THERAPEUTIC INDICATIONS :
SPEDIFEN is indicated for relieving pain of various etiology: headache, pain after tooth extraction and postoperative pain, as well as for the treatment of primary dysmenorrhea.
SPEDIFEN is also indicated for the relief of signs and symptoms of rheumatoid arthritis and *osteoarthritis*, as well as for the musculoskeletal and traumatic alterations implying pain and inflammation

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties:
General properties
Pharmacotherapeutic group: Antiinflammatory and anti-rheumatic products, non-steroids, Propionic acid derivatives.
ATC code: M01AE01.
Ibuprofen is a synthetic analgesic-antiinflammatory drug with a marked antipyretic action.
Mechanism of action
Ibuprofen is the first phenylpropionic acid derivative. It is a prostaglandin synthetase inhibitor with analgesic, antipyretic and anti-inflammatory properties.
It possesses a non-narcotic analgesic activity.
The mechanism of action of ibuprofen (in situ formation of L-arginine salt) is linked to the reversible inhibition of the COX enzyme, responsible for conversion of arachidonic acid into cyclic endoperoxydes, hence reducing the synthesis of thromboxane (TXA2), prostacyclines (PGI2) and prostaglandines (PG).
Pharmacodynamic effects
Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics studies

show that when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81mg), a decreased effect of ASA 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 cardio protective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use. (See Interaction with other medicinal products and other forms of interaction).

Pharmacokinetic properties:
Absorption
After oral administration, SPEDIFEN is rapidly absorbed by the GI tract. Maximal ibuprofen plasma levels by approximately 40 µg/mL and 60 µg/mL are achieved at approximately 35 minutes after administration of SPEDIFEN 400 and 600 tablet, and by approximately 56 µg/mL and 60 µg/mL after SPEDIFEN 400 and 600 mg granules for oral solution, respectively.
Concomitant administration with food does not influence the extent of absorption but delays the absorption of approx. 1 hour, which results in a lower Cmax (approx. 50%).
Distribution
After absorption, ibuprofen is conjugated to plasma-proteins for about 99% and is mainly distributed throughout the plasma compartment. It diffuses slowly into the synovial spaces and is eliminated more slowly from these spaces than it is from the plasma.
Biotransformation
Ibuprofen is metabolised in the liver mainly by hydroxylation and carboxylation of the isobutyl group. The metabolites have no known pharmacological activity.
Elimination
The plasma half-life is 1-2 hours. Over 90% of dosage can be found in the urine as metabolites and their conjugates. Less than 1% is excreted unchanged in the urine.
Linearity/non-linearity
Ibuprofen shows non-linear kinetics inasmuch as total plasma AUC increases less than proportionately with the given dose. Non-linearity is attributed to saturation of plasma protein binding.

Preclinical safety data:
Non-clinical data reveal no special hazard for humans but for lesions and ulcerations in the gastro-intestinal tract based on conventional studies of safety pharmacology and repeated dose toxicity, genotoxicity, carcinogenic potential.
With respect to toxicity to reproduction and development, ibuprofen inhibited ovulation in hCG-stimulated rabbits and impaired implantation in different animal species (rabbit, rat, and mouse). Reproductive toxicity studies conducted in rats and rabbits have demonstrated that ibuprofen passes the placenta; for maternally toxic doses, an increased incidence of malformations (e.g. ventricular septal defects) was observed.

No juvenile animal studies have been performed.
Because in suckling and weanling rats and in newborn rabbits ibuprofen suppresses the renal COX2 and vasodilator prostanoids, which are important regulators of renal development and function, this implies possible severe adverse renal effects when ibuprofen is administered during early postnatal life

POSOLOGY AND ADMINISTRATION ROUTE:
Dosage for adults:
The main recommended posology is 1200 mg/day, divided into 3-4 single administrations. Should gastric disturbances appear after drug ingestion, then the administration can be performed by drinking concomitantly some milk or during meals.

In case of rheumatoid arthritis, a higher dosage may be required but in any case, it is recommended not to exceed 2400 mg Ibuprofen a day, by considering that the lowest possible effective dose is to be administered.
In case of primary dysmenorrhea the recommended dose is 400 mg every 4 hours up to pain relief, always considering the lowest possible effective dosage.
For elderly patients, the posology is to be established by the physician, as a possible usual dose reduction may be needed. In case of kidney failure, the dosage must be adequately adjusted, being the drug eliminated preferably through renal excretion.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see Posology and method of administration and GI and cardiovascular risk below)

GI Effects
The use of SPEDIFEN with Concomitant NSAIDs, including COX-2 selective inhibitors should be avoided.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs which may be fatal (See Posology and method of administration)

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 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 Contraindications), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (See Interactions with other medicinal products and other forms of interaction).

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, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetyl salicylic acid (See Interactions with other medicinal products and other forms of interaction).

When GI bleeding or ulceration occurs, 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 Undesirable effects).

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. Fluid retention, hypertension and oedema have been reported in association with NSAIDs therapy.
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 event (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200 mg/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 (2400 mg/day) should be avoided.
Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Cases of Kounis syndrome have been reported in patients treated with SPEDIFEN . 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 generalised 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 SPEDIFEN should be withdrawn immediately and an alternative treatment considered (as appropriate).

Masking of symptoms of underlying infections
SPEDIFEN 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 SPEDIFEN 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 worse

Other effects

Caution is required in patients with coagulation disorders and liver, cardiac or kidney insufficiency.

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

Risks of long-term habitual use of analgesic are headache and analgesic nephropathy.

Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.

Caution is required in patients with systemic lupus erythematosus or other collagen diseases.

There is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Patients who experience visual disturbances during ibuprofen therapy should discontinue the treatment and have an ophthalmologic examination.

NSAIDs may produce an increase of liver function test results.

SPEDIFEN 400 mg Film-Coated Tablet
Sucrose
This medicinal product contains 16.7 mg sucrose per dose unit. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.
Sodium
This medicinal product contains 302 mg sodium per dose unit. To be taken into consideration by patients on a controlled sodium diet.

ADVERSE EVENTS :
Undesirable effects are primary linked to the pharmacological effect of ibuprofen on prostaglandin synthesis.
The most commonly reported adverse events effect the gastrointestinal tract, ranging from nausea and dyspepsia to serious bleeding or activation of peptic ulcer (see special warnings and precautions for use).

Bullous reaction including Steven-Jhonson's syndrome and toxic epidermal Necrolysis where observed very seldom.

Oedema, hypertension, and cardiac failure have been reported in association with NSAIDs treatment. Clinical studies suggest that use of ibuprofen, particularly at high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infraction or stroke) (see Special Warnings and precaution for use)

In the table below adverse reactions are listed by system organ class , and 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) and not known (cannot be estimated from the available data)
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Sytem Organ Class	**Frequency**
Blood and lymphatic system disorders	
Thrombocytopenia, Agranulocytosis, Aplastic Anaemia	rare
Anaemia	Not Known
Immune system disorders	
Allergic reaction	Uncommon
Anaphylaxis	Rare
Anaphylactic Shock	Not Known
Nervous system Disorders	
Headache, dizzines	Common
Meningitis Aseptic	Not Known
Eye Disorders	
Visual Disturbance	Rare
Papilloedema	Not Known
Ear and Labyrinth Disorders	
Ear Disorder	Rare
Cardiac Disorders	

Cardiac Failure	Not Known
Kounis syndrome	Not Known
Vascular Disorders	
Arterial thrombosis, Hypertension, Hypotension	Not Known
Respiratory, Thoracic and Mediastinal Disorders	
Asthma, Aggravated Asthma, Bronchospasm, Dyspnea	Uncommon
Throat irritation	Not known
Gastrointestinal Disorders	
Dyspepsia, Diarrhoea	Very Common
Abdominal Pain, nausea, Flatulence	Common
Peptic Ulcer, Gastrointestinal, Haemorrhage, Vomiting, malaena, gastritis	Uncommon
Gastrointestinal Perforation, Constipation, Haematemesis, Ulcerative stomatitis, Colitis Aggravated, Chron's Disease Aggravated	Rare
Anorexia	Not Known
Hepato-biliary Disorders	
Hepatic disorders	Rare
Liver Injury, Hepatitis, Jaundice	Not known
Skin and Subcutaneous Tissue Disorders	
Skin Disorders, Rash	Common
Angioedema, Purpura, Pruritus, Urticaria	Uncommon
Severe cutaneous adverse reactions (SCARs) (including Erythema Multiforme, Exfoliative Dermatitis, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis).	Very Rare
Photosensitivity reaction, Skin Reaction aggravated	Not Known
Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)	Not known
Acute generalised exanthematous pustulosis (AGEP)	Not known
Renal and urinary disorders	
Hematuria	Rare
Acute Renal Failure, Interstitial Nephritis, Papillary Necrosis	Very Rare
General Disorders and Administration Site Conditions	

Oedema	Not known
Investigations	
Liver Function Test Abnormal	Rare
Renal Function Test Abnormal	Not Known

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 :
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat,
Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR.

CONTRAINDICATIONS :
- Hypersensitivity to the active substance “ibuprofen” or to any of the excipients of this medicinal product. (See List of Excipients)
- History of hypersensitivity reactions (e.g. bronchospasm, asthma, rhinitis or urticaria) in response to acetylsalycilic acid (ASA) or other non-steroidal anti-inflammatory drugs (NSAIDs).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Other active bleeding like cerebrovascular bleedings or colitis ulcerosa.
- Severe kidney and/or liver insufficiency.
- Hemorrhagic diathesis
- Third trimester of pregnancy (see section 4.6 Pregnancy and Lactation).
- Severe heart failure (NYHA Class IV)

PREGNANCY AND LACTATION :
Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data form epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformations and gastroschisis in the new borns after the use of prostaglandin synthesis inhibitor in the early phase of pregnancy. The absolute risk on cardiac malformation was increase from less than 1% to about 1.5%. It is assumed that the risk increases with dose and duration therapy. Administration of prostaglandin synthesis inhibitors to animal resulted in an increased pre- and post- implantation loss and embryo fetal lethality. Moreover, an increased incidence of various malformations, including cardiovascular defects, has been reported in animals receiving prostaglandin, synthesis inhibitors during the period of organogenesis.
From the 20th week of pregnancy onward, SPEDIFEN 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, SPEDIFEN should not be given unless clearly necessary. If SPEDIFEN 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 SPEDIFEN for several days from gestational week 20 onward. SPEDIFEN 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 (with premature cosntuction/ closure of the ductus arterious and pulmonary hypertension)
- Renal dysfunction (see above), which may progress to renal failure with oligo-hydroamniosis; and the mother and the child, at the end of pregnancy, may be exposed to.
- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even after very low doses
- Inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, SPEDIFEN is contraindicated during the third trimester of pregnancy (see contraindications)

Lactation
Ibuprofen and its products of decomposition/ metabolites are excreted in human milk, but at therapeutic doses of SPEDIFEN no effects on the breastfed newborns/infants are anticipated. As harmful effects on the infant are not yet known, it is not generally necessary to interrupt breast-feeding for short-term treatment with recommended dose for mild to moderate pain and fever.

Fertility
If ibuprofen is used by a woman attempting to conceive the dose should be kept as low and duration of treatment as short as possible.

EFFECTS ON THE DRIVING CAPABILITY AND MACHINES USE :
Dizziness and headache have been reported which may affect the patient's ability to drive or to operate machinery.
Single administration or short term use of ibuprofen does not usually warrant the adoption of any special precautions.
Therefore, SPEDIFEN has minor influence on these abilities

MEDICAL AND OTHER INTERACTIONS :

- Acetylsalycilic acid : Concomitant administration of ibuprofen and Acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects. Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see Pharmacodynamic properties)
- Diuretics : The efficacy of furosemide and thiazide diuretics can be decreased, probably due to sodium retention related to an inhibition of prostaglandin synthesis in the kidneys.
- Corticosteroid : increase risk of gastrointestinal ulceration or bleeding (see special warnings and precaution for use)

- Anti-coagulants : NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see special warning and precautions for use)
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) : increased risk of gastrointestinal bleeding (see special warning and precautions for use)
- Anti-hypertensives agents : Ibuprofen may diminish the effects of anti-hypertensives. Consequently, the concomitant use of NSAIDs and ACE-Inhibitors or beta-blocking agents may be associated with a risk of acute renal failure.
- Digoxin, phenytoin,lithium : in the literature individual cases of increase plasma levels of digoxin, phenytoin and lithium due to ibuprofen have been described.
- Other non-steroid anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 selective inhibitors : ibuprofen (like other NSAIDs) should be used with caution in combination with acetylsalicylic acid or other NSAIDs and systemic corticosteroids : this may increase the risk of adverse drug reactions in the gastro intestinal tract
- Methotrexate : Ibuprofen can increase methotrexate plasma levels
- Zidovudine : Concurrent treatment of zidovudine and ibuprofen can increase the risk of haemarthoses and haematoma in HIV (+) haemophilic patients
- Tacrolimus : Concurrent use of ibuprofen and tacrolimus can increase the risk of nephrotoxicity, due to the reduction of the renal prostaglandins synthesis
- Hypoglycaemics agent : Ibuprofen increases hypoglycemic effects of oral hypoglycemic agents and insulin. It may be necessary to adjust the dosage
- Cyclosporine : Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) may result in increased risk of cyclosporine nephrotoxicity effect
- Voriconazole or Fluconazole : Concurrent use of ibuprofen may result in increased ibuprofen exposure and plasma concentration.
- Mifepristone : Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) may result in increased exposure to the NSAID

A decrease in the efficacy of mifepristone can theoretically occur due to the antiprostaglandin properties of NSAIDs. Studies on the effect of single or repeated ibuprofen administration starting on the day prostaglandin administration (or as needed) did not find evidence of an adverse influence on the action of mifepristone, nor or the overall clinical efficacy of the pregnancy termination protocol.

- Quinolone antibiotics : Concurrent use of non-steroidal use of non-steroidal anti-inflammatory drugs (NSAIDs) may result in an increased risk of seizures.
- Herbal Extract : Gingko biloba may potentiate the risk of bleeding with NSAIDs
- Aminoglycosides : NSAIDs may decrease the excretion of aminoglycosides

Interactions with diagnostic test results :

- Bleeding time (may prolong bleeding time until 1 day after discontinuation of theraphy)
- Serum glucose concentration (may decrease)
- Creatinine Clearance (may decrease)
- Haematocrit or haemoglobin (may decrease)
- BUN, serum creatinine concentration and kaliemia (may increase)
- Liver function test (may occur elevation of transaminases)

OVERDOSE:

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

Symptoms
In general, overdose symptoms include nausea, gastralgia, vomiting (blood) and diarrhoea (blood), dizziness, spasms, nystagmus and diplopia, headache and tinnitus. In case of severe

intoxication also renal function disorders, hypotension, decrease of consciousness and coma (it is not clear whether the renal function disorder is caused by the intoxication or by the concurrent hypotension).
In serious poisoning metabolic acidosis may occur

Management of overdose
There is no specific antidote for ibuprofen. The stomach should be emptied as soon as possible. If possible, the patient should vomit. If the patient is unconscious, gastric lavage and correction of severe electrolyte abnormalities should be considered.

SHELF-LIFE AND STORAGE :
3 years, at temperature below 30°C

Package size :
Box of 5 blister @ 6 film-coated tablet

HARUS DENGAN RESEP DOKTER

Manufactured by :
Zambon S.p.A.
Vicenza – Italy

Imported by :
PT. Tunggal Idaman Abdi
Jakarta – Indonesia

Marketed by :
PT. Zambon Indonesia
Jakarta – Indonesia

Reg. No : DKI1074300417A1