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

Informasi untuk Pasien
SPEDIFEN
Ibuprofen
400 mg
Tablet Salut Selaput

Baca informasi di leaflet ini dengan teliti karena mengandung informasi yang penting untuk Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya lagi.
- Konsultasikan dengan dokter atau apoteker jika Anda memiliki keraguan.
- Obat ini diresepkan hanya untuk Anda. Jangan memberikannya ke orang lain. Hal ini dapat membahayakan, meski mereka memiliki gejala yang sama dengan Anda.
- Jika mengalami efek samping, termasuk efek samping yang tidak tertera dalam leaflet ini, segera beritahukan dokter atau apoteker Anda. Lihat bagian 4.

Apa yang ada di Leaflet ini:

1. Apa SPEDIFEN dan Kegunaannya

Obat ini mengandung bahan aktif Ibuprofen dan dalam bentuk garam L-Arginine, yang termasuk dalam kelompok obat anti inflamasi non-steroid (*non-steroidal anti inflammatory drugs / NSAID*) yang digunakan untuk mengurangi nyeri (analgesik) dan peradangan (anti-inflamasi), menurunkan demam (antipiretik)
SPEDIFEN digunakan untuk mengobati nyeri yang disebabkan oleh sakit kepala, nyeri setelah cabut gigi, nyeri pasca operasi, serta pengobatan nyeri haid/menstruasi.
SPEDIFEN juga digunakan untuk mengurangi tanda dan gejala *rheumatoid arthritis* dan *osteoarthritis*, juga pengobatan nyeri dan peradangan akibat cedera muskuloskeletal.

2. Apa yang perlu diketahui sebelum menggunakan SPEDIFEN

Jangan gunakan SPEDIFEN Jika Anda:
- Memiliki alergi terhadap Ibuprofen, obat-obatan serupa atau salah satu kandungan dalam obat ini (lihat bagian bahan tambahan)
- Memiliki riwayat reaksi alergi (sesak nafas, asma, rhinitis, urtikaria) terhadap asam salisilat atau obat golongan NSAID lainnya.
- Memiliki riwayat perdarahan atau luka pada saluran pencernaan yang terkait dengan penggunaan NSAID.
- Memiliki riwayat kekambuhan perdarahan/tukak lambung (2 atau lebih kejadian tukak lambung atau perdarahan)
- Menderita penyakit perdarahan lain seperti perdarahan pembuluh darah di otak ataupun kolitis ulseratif.
- Menderita insufisiensi ginjal dan atau hati yang parah
- Trimester 3 kehamilan (lihat bagian kehamilan dan laktasi)
- Menderita penyakit gagal jantung (NYHA class IV)

Peringatan dan Perhatian
Gunakan dosis efektif paling rendah dengan jangka waktu pengobatan yang paling singkat untuk mengurangi risiko efek yang tidak diinginkan.

Risiko di Saluran Pencernaan

Perdarahan di saluran cerna, tukak/ulser dan perlukaan/perforasi yang mungkin serius dapat terjadi tanpa gejala maupun tanpa riwayat penyakit saluran cerna. Jika Anda memiliki riwayat tukak lambung, risiko peradahan, ulser, dan perlukaan dapat meningkat seiring dengan dosis NSAIDs yang digunakan. Dokter akan meresepkan obat lain yang dapat melindungi lambung Anda, seperti, misoprostol atau obat golongan PPI, terutama jika Anda menggunakan obat lain (contoh: aspirin atau obat lain yang dapat meningkatkan risiko saluran cerna).

Gunakan SPEDIFEN dengan hati-hati dan beritahukan kepada dokter dan apoteker Anda jika:

- Anda sudah mengkonsumsi obat anti inflamasi lain (termasuk golongan COX-2 selektif inhibitor)
- Anda menggunakan obat-obatan yang dapat meningkatkan risiko ulser dan perdarahan, seperti kortikosteroid, antikoagulan seperti warfarin atau heparin, SSRI atau agen anti pembekuan darah seperti aspirin
- Anda pernah menderita penyakit saluran cerna (kolitis ulseratif, *crohn's disease*)

Lansia

Jika Anda berusia lanjut (lansia), Anda lebih berisiko mengalami efek samping, terutama perdarahan dan perlukaan di saluran cerna, yang mungkin berakibat fatal. Risiko perdarahan, ulser atau perforasi meningkat seiring dosis NSAIDs. Maka gunakan SPEDIFEN dengan dosis serendah mungkin dan durasi sesingkatnya. Dokter mungkin akan meresepkan Anda dengan obat tertentu untuk melindungi lambung Anda, terutama jika Anda juga mengkonsumsi obat-obatan lain (contoh: asam salisilat atau obat lain yang dapat meningkatkan risiko saluran cerna).

Beritahukan kepada dokter atau apoteker Anda jika Anda mengalami gejala saluran cerna di awal pengobatan dengan SPEDIFEN.

Segera hentikan penggunaan SPEDIFEN jika Anda mengalami perdarahan saluran cerna dan segera ke dokter atau rumah sakit untuk mendapat penanganan.

Risiko stroke dan infark miokardia:

Obat-obat anti inflamasi dan penghilang nyeri seperti SPEDIFEN dapat dikaitkan dengan peningkatan risiko serangan jantung (infark miokardia) atau stroke, terutama jika diberikan dengan dosis tinggi. Jangan melebihi dosis atau durasi terapi yang direkomendasikan. Pernah dilaporkan adanya gejala kardiovaskular akibat reaksi alergi setelah pemakaian SPEDIFEN (sindrom kounis).

Beritahukan kepada dokter atau apoteker Anda sebelum menggunakan SPEDIFEN jika:

- Anda memiliki masalah jantung, terutama serangan jantung, angina (nyeri dada) atau jika Anda pernah terkena serangan jantung, pernah menjalani operasi *coronary bypass*, menderita penyakit arteri perifer atau stroke (termasuk "mini-stroke" atau serangan iskemik transien)

- Anda memiliki tekanan darah tinggi, diabetes, kolesterol tinggi, riwayat keluarga dengan penyakit jantung atau stroke, atau jika Anda perokok.

Reaksi pada kulit

Terdapat laporan terkait reaksi kulit yang serius akibat penggunaan SPEDIFEN. Segera hentikan penggunaan SPEDIFEN dan segera dapatkan penanganan medis jika Anda mengalami ruam kulit, lesi pada selaput lender, iritasi atau tanda alergi lain, karena hal tersebut dapat menjadi gejala awal reaksi kulit yang serius. Reaksi kulit yang berat (*severe cutaneous adverse reaction*) seperti *exfoliative dermatitis, eritema multiform, Stevens-Johnson syndrom, Toxic epidermal necrolysis, sindroma DRESS, dan AGEP* yang mungkin fatal atau mengancam jiwa pernah dilaporkan terjadi setelah penggunaan ibuprofen.

Infeksi

SPEDIFEN dapat menutupi gejala infeksi seperti demam dan nyeri yang mungkin menyebabkan pengobatan untuk infeksi tersebut tertunda dan bisa jadi meningkatkan risiko komplikasi. Hal ini diketahui terjadi pada pneumonia yang disebabkan oleh bakteri dan infeksi bakteri di kulit seperti cacar air. Jika Anda menggunakan SPEDIFEN untuk mengurangi gejala infeksi seperti demam atau nyeri akibat infeksi namun gejala tersebut tidak berkurang atau semakin memburuk, segera konsultasikan ke dokter. Gunakan ibuprofen dengan hati-hati dalam kondisi infeksi.

Efek lainnya

Gunakan dengan hati-hati pada pasien dengan gangguan penggumpalan darah dan gangguan hati, jantung atau insufisiensi ginjal.

Gunakan dengan hati-hati ketika memulai pengobatan dengan ibuprofen pada pasien yang mengalami dehidrasi berat.

Sakit kepala dan nefropati analgesik merupakan risiko penggunaan analgesik jangka panjang.

Bronkospasme dapat terjadi pada pasien dengan riwayat asma bronkial atau alergi

Jika Anda menderita lupus erythematosus sistemik atau penyakit kolagen lainnya, gunakan SPEDIFEN dengan hati-hati.

Terdapat data yang menunjukkan obat penghambat siklooksigenase/sintesis prostaglandin dapat memengaruhi ovulasi yang mungkin dapat mengganggu kesuburan wanita. Efek ini bersifat sementara dan akan kembali normal setelah penggunaan obat dihentikan.

Segera hentikan penggunaan Ibuprofen jika Anda mengalami gangguan penglihatan selama terapi, dan segera periksakan keadaan Anda ke dokter.

NSAID dapat mempengaruhi hasil laboratorium tes fungsi hati.

Penggunaan SPEDIFEN dapat memengaruhi hasil pemeriksaan diagnostik tertentu.

Obat-obatan lain dan SPEDIFEN

Beritahukan kepada dokter atau apoteker jika Anda sedang, akan atau atau pernah menggunakan obat-obatan lain, karena mungkin dapat mempengaruhi efektivitas SPEDIFEN.

SPEDIFEN, sebagaimana obat-obatan sejenisnya (NSAID, Analgesik, Antipiretik) dapat menimbulkan reaksi alergi (hipersensitivitas).

Jangan gunakan SPEDIFEN jika Anda sudah menggunakan obat anti inflamasi lain (analgesik, anti piretik, dan NSAID lainnya seperti asam salisilat /aspirin), karena dapat meningkatkan risiko efek samping. Jika Anda menggunakan produk yang mengandung asam salisilat untuk kondisi jantung Anda, jangan konsumsi bersama dengan SPEDIFEN karena dapat menurunkan efek proteksi jantung dari obat lain.

Gunakan obat ini dengan hati-hati dan beritahukan kepada dokter jika Anda menggunakan salah satu obat dalam daftar berikut:

- Obat untuk mengurangi inflamasi dan mengobati alergi (kortikosteroid oral), karena SPEDIFEN dapat meningkatkan risiko ulser atau perdarahan di saluran cerna;
- Diuretik: Efektivitas furosemid dan diuretik tiazid dapat menurun, kemungkinan karena retensi natrium yang berhubungan dengan penghambatan sintesis prostaglandin di ginjal;
- Obat yang memiliki efek anti penggumpalan darah (contohnya asam salisilat/aspirin, warfarin, dan ticlopidine), SPEDIFEN dapat meningkatkan efek pengenceran darah dari obat-obat tersebut. Dokter mungkin akan melakukan pemeriksaan tertentu untuk pertimbangan penyesuaian terapi. SPEDIFEN juga mungkin meningkatkan risiko perdarahan jika digunakan bersamaan dengan obat-obatan tersebut;
- Obat-obatan penurun tekanan darah (diuretik, ACE inhibitor seperti kaptopril, beta-blocker seperti atenolol, angiotensin-II reseptor antagonis seperti losartan). SPEDIFEN mungkin mengubah efek obat-obat tersebut jika diminum bersamaan. Selain itu jika Anda menderita masalah ginjal, terutama jika Anda berusia lanjut atau dehidrasi, SPEDIFEN bisa jadi memperparah kondisi anda jika digunakan bersamaan dengan ACE-inhibitor atau angiotensin-II reseptor antagonis. Dalam kasus ini, Anda perlu mengkonsumsi cairan dalam jumlah tertentu. Dokter Anda mungkin akan mengecek fungsi ginjal Anda secara berkala;
- Obat-obatan untuk terapi depresi dan gangguan kecemasan (*selective serotonin reuptake inhibitor*), SPEDIFEN mungkin meningkatkan risiko saluran cerna;
- Obat-obatan untuk terapi gangguan mental dan mengandung litium dan fenitoin. SPEDIFEN dapat meningkatkan konsentrasi obat tersebut dalam darah;
- Obat-obatan seperti digoksin yang digunakan untuk menangani masalah jantung. SPEDIFEN dapat meningkatkan konsentrasi obat tersebut dalam darah;
- *Non-steroidal anti-inflammatory drugs* (NSAIDs), termasuk inhibitor selektif COX-2. SPEDIFEN harus digunakan dengan hati-hati dengan NSAID lain karena dapat meningkatkan reaksi kejadian tidak diinginkan di saluran pencernaan;
- Obat-obatan dengan metotreksat yang digunakan untuk mengontrol proliferasi sel darah (leukemia), untuk pengobatan gangguan inflamasi kulit kronis (psoriasis) dan gangguan inflamasi sendi kronis yang berhubungan dengan gangguan kulit (psoriatic arthritis). SPEDIFEN dapat meningkatkan plasma level dari metrotreksat;
- Obat-obatan dengan zidovudine yang digunakan untuk pengobatan HIV, SPEDIFEN dapat meningkatkan risiko perdarahan di sendi dan otot pada pasien HIV(+);
- Obat-obatan dengan siklosporin dan trakrolimus, yang digunakan untuk mencegah penolakan transplan pasca transplantasi hati, ginjal maupun jantung. SPEDIFEN dapat meningkatkan risiko toksisitas renal;
- Obat-obatan untuk menurunkan kadar gula dalam darah, hipoglikemia, dan insulin. Penyesuaian dosis mungkin dibutuhkan;
- Obat-obatan dengan siklosporin yang digunakan untuk menurunkan aktivitas imun pada pasien autoimun. SPEDIFEN dapat meningkatkan risiko toksisitas renal;
- Obat anti-fungal yang mengandung voriconazole dan fluconazole. Penyesuaian dosis SPEDIFEN mungkin diperlukan;

- Obat-obatan mengandung mifepristone yang digunakan untuk mencegah kehamilan: dosis SPEDIFEN mungkin perlu disesuaikan. Efikasi dari mifepristone, secara teori, mungkin dapat berkurang;
- Obat-obatan untuk pengobatan infeksi bakteri, seperti antibiotik golongan quinolone, karena SPEDIFEN dapat meningkatkan risiko kejang;
- Obat-obatan untuk pengobatan infeksi bakteri, seperti aminoglikosida, karena SPEDIFEN dapat menurunkan ekskresinya;
- Produk yang mengandung ginkgo biloba, karena SPEDIFEN dapat meningkatkan risiko perdarahan.

Penggunaan SPEDIFEN mungkin dapat mempengaruhi atau terpengaruhi obat-obatan lain. Anda harus selalu konsultasikan pada dokter atau apoteker sebelum menggunakan SPEDIFEN dengan obat-obatan lain.

Kehamilan, laktasi, dan kesuburan

Jika Anda hamil, menduga hamil, atau sedang merencanakan kehamilan, ataupun sedang menyusui, sampaikan pada dokter atau apoteker Anda sebelum menggunakan obat ini.

Kehamilan

Pastikan Anda tidak sedang hamil sebelum memulai pengobatan; hentikan pengobatan jika Anda hamil.

Jangan gunakan SPEDIFEN di trimester 3 kehamilan karena dapat membahayakan calon bayi Anda atau menimbulkan masalah saat persalinan, antara lain dapat menyebabkan masalah ginjal dan jantung bagi calon bayi Anda. Selain itu dapat meningkatkan risiko perdarahan pada Anda dan bayi Anda, serta memperpanjang masa persalinan lebih lama dari hari perkiraan lahir. Jangan gunakan SPEDIFEN selama 6 bulan awal kehamilan kecuali sangat diperlukan dan diresepkan oleh dokter Anda. Jika Anda membutuhkan pengobatan dalam periode tersebut atau sedang merencanakan kehamilan, gunakan dosis paling rendah dengan durasi paling singkat. Jika digunakan lebih dari beberapa hari sejak 20 minggu kehamilan, SPEDIFEN dapat menyebabkan masalah ginjal pada calon bayi Anda yang mengakibatkan penurunan kadar air ketuban disekitar bayi (*oligohydramnios*) atau penyempitan pembuluh darah (*ductus arteriosus*) pada bayi Anda. Jika Anda membutuhkan pengobatan lebih dari beberapa hari, dokter akan merekomendasikan pengawasan tambahan.

Menyusui

Hindari penggunaan SPEDIFEN saat menyusui .

Kesuburan

Jangan gunakan SPEDIFEN jika Anda menderita masalah kesuburan.

Berkendara dan mengoperasikan mesin

Obat ini dapat menyebabkan kantuk, dan sakit kepala yang dapat mempengaruhi kemampuan Anda dalam berkendara dan mengoperasikan mesin.

SPEDIFEN mengandung sukrosa dan natrium.

Obat ini mengandung 16.7 mg sukrosa, yang merupakan sejenis gula. Jika dokter pernah memberitahu bahwa Anda intoleran terhadap jenis gula tertentu, konsultasikan pada dokter sebelum menggunakan obat ini.

Setiap tablet SPEDIFEN mengandung 302 mg natrium (komponen utama dari garam dapur/garam meja), agar dipertimbangkan jika Anda perlu mengontrol asupan natrium Anda.

Cara Penggunaan SPEDIFEN

Selalu konsumsi obat ini sesuai arahan dokter dan apoteker Anda, pastikan dengan dokter atau apoteker jika Anda tidak yakin.

Dewasa

Dosis yang dianjurkan 1200mg/hari yang dibagi dalam 3-4 kali pemberian, atau sesuai resep dokter.
Jika Anda kesulitan menelan obat, SPEDIFEN dapat dikonsumsi pada waktu makan.

Apabila Anda menggunakan SPEDIFEN untuk terapi *rheumatoid arthritis*, dosis yang lebih tinggi mungkin diperlukan, dianjurkan tidak melebihi 2400 mg atau 6 tablet ibuprofen per hari dengan mempertimbangkan pemberian dosis efektif serendah mungkin.

Jika Anda menggunakan SPEDIFEN untuk pengobatan dismenor primer (nyeri haid), dosis yang direkomendasikan yaitu 400 mg setiap 4 jam untuk mengurangi nyeri. Selalu gunakan dosis efektif terendah.

Penggunaan pada pasien lansia
Konsultasikan kepada dokter karena mungkin diperlukan pengurangan dosis.

Penggunaan pada pasien dengan penurunan fungsi ginjal, hati dan fungsi jantung
Selalu sampaikan pada dokter Anda karena pengurangan dosis mungkin diperlukan.
Jika Anda menderita gangguan ginjal, hati atau jantung yang parah, penggunaan SPEDIFEN tidak dianjurkan.

Jika Anda mengkonsumsi SPEDIFEN lebih dari yang dianjurkan.
Jika Anda mengkonsumsi SPEDIFEN lebih dari yang seharusnya secara sengaja maupun tidak disengaja, selalu hubungi dokter atau rumah sakit terdekat untuk mendapatkan penanganan terkait risiko dan tindakan yang perlu diambil.
Gejala overdosis antara lain mual, sakit perut, muntah (yang mungkin terdapat darah), diare, pusing, kejang, gangguan pengelihatan (nystagmus dan diplopia), sakit kepala dan telinga berdenging/ tinnitus.
Gejala serius dapat terjadi, antara lain gangguan renal, penurunan tekanan darah, penurunan kesadaran.
Dalam kasus overdosis yang signifikan kegagalan ginjal dan kerusakan hati mungkin terjadi.
Penggunaan jangka panjang pada dosis lebih dari yang dianjurkan dapat menimbulkan gangguan pada ginjal dan hipokalemia.

Jika telah tertelan dalam jumlah besar, segera kosongkan isi perut dengan memancing muntah, secepatnya dalam 1 jam pertama setelah konsumsi jumlah besar.

Selalu konsultasikan dengan dokter atau apoteker Anda jika ragu menggunakan SPEDIFEN.

3. Kemungkinan efek samping

Seperti obat-obatan lainnya, obat ini dapat menyebabkan efek samping, meski tidak semua orang mungkin mengalaminya.

Efek samping berikut mungkin terjadi:

Sangat umum (dapat terjadi pada lebih dari 1 dari 10 orang)
- Masalah pencernaan (dyspepsia); diare

Umum (dapat terjadi sampai 1 dari 10 orang)
- Nyeri perut, mual, kembung;
- Sakit kepala, pusing;
- Ruam, gangguan di kulit

Tidak umum (dapat terjadi pada 1 dari 100 orang)
- Perlukaan di perut atau usus (tukak lambung atau perdarahan, yang mungkin fatal, terutama pada lansia
- Muntah
- Adanya darah pada feses (melaena)
- Inflamasi di lambung (gastritis)
- Gatal, iritasi kulit (urtikaria, exanthem), masalah kulit serius terkait perdarahan (purpura)
- Bengkak di wajah, bibir, mulut, lidah, atau tenggorokan yang dapat menyebabkan kesulitan menelan dan bernapas
- Reaksi alergi
- Kesulitan pernapasan (asma, peningkatan keparahan asma, bronkospasm, dispnea)

Jarang (dapat terjadi 1 dari 1000 orang)
- Perlukaan di saluran cerna
- Konstipasi
- Muntah darah
- Inflamasi di rongga mulut terkait lesi (*ulserative stomatitis*)
- Perburukan beberapa penyakit saluran cerna (kolitis, *Crohn's disease*)
- Gangguan pendengaran, dengung di telinga (t*innitus*)
- Gangguan pengelihatan (pandangan berbayang dan amblyopia)
- Gangguan level platelet, sel darah putih, dan sel darah merah (trombositopenia, agranulositosis, anemia aplastic, anemia hemolitik, granulositopenia)
- Adanya darah di urin (hematuria)
- Masalah hati
- hasil tes fungsi hati yang abnormal (aktivitas transaminase tinggi)
- reaksi alergi yang parah (anafilaksis)

Sangat jarang (dapat terjadi sampai 1 dari 10,000 orang)
- Gangguan kulit parah (*severe cutaneous adverse reactions (scars)*, *exfoliative dermatitis, steven-johnson syndrome, erythema multiforme, toxic epidermal necrolysis)*;
- Gangguan ginjal (interstitial nefritis, papilari nekrosis, cidera ginjal, termasuk bentuk akut)

Tidak diketahui (frekwensi tidak bisa diperkirakan dari data yang tersedia)
- Hilang nafsu makan dan berat badan (anorexia)
- Pembengkakan pada bagian tubuh tertentu akibat akumulasi cairan (edema)

- Masalah jantung (gagal jantung)
- Kounis syndrome
- Peningkatan tekanan darah (hipertensi)
- Gangguan sirkulasi darah (thrombosis)
- Penurunan tekanan darah (hipotensi)
- Infeksi pada membrane disekitar otak tanpa infeksi bakteri (aseptic meningitis)
- Pembengkakan di antara saraf optik dan mata (papiloedema)
- Reaksi obat dengan eosinophil dan gejala sistemik (*dress syndrome*) yang gejalanya termasuk, ruam, demam, pembengkakan nodul limfa, dan peningkatan eosinophil
- Reaksi yang tidak terduga dan berlebihan setelah terpapar sinar matahari (reaksi fotosensitivitas)
- Anemia
- Pengeluaran garam dan cairan yang tidak baik yang mengakibatkan pembengkakan (edema)
- Inflamasi hati (hepatitis), perusakan hati, penyakit kuning (*jaundice)*
- Gangguan hasil tes fungsi ginjal
- Reaksi klinis yang parah di area yang terkena allergen (syok anafilaktik)
- Sakit tenggorokan (iritasi tenggorokan)
- Ruam merah bersisik yang meluas, dengan benjolan di bawah kulit dan lepuh, terutama terlokalisasi pada lipatan kulit, batang tubuh dan ekstremitas atas, disertai demam pada awal pengobatan (pustulosis eksantematosa generalisata akut).
  Segera hentikan penggunaan SPEDIFEN jika Anda mulai mengalami gejala-gejala tersebut dan segera hubungi dokter Anda.

Pelaporan efek samping

Jika Anda mengalami efek samping, termasuk efek samping yang tidak tercantum dalam leaflet ini, hubungi dokter atau apoteker Anda. Anda juga dapat melaporkan kepada indonesia.localpv@zambongroup.com. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

Dengan melaporkan efek samping, Anda dapat membantu menambahkan informasi terkait keamanan obat ini.

4. Cara penyimpanan SPEDIFEN

Jauhkan dari jangkauan anak anak
Jangan gunakan melewati tanggal kedaluwarsa yang tertera pada kemasan. Tanggal kedaluwarsa merujuk pada hari terakhir dari bulan yang tertera.

Simpan di bawah suhu 30˚C.

Jangan membuang obat apa pun ke dalam air limbah atau bersama limbah rumah tangga. Tanyakan kepada apoteker Anda tentang cara membuang obat-obatan yang tidak lagi Anda gunakan. Ini akan membantu melindungi lingkungan.

5. Isi kemasan dan informasi lainnya

SPEDIFEN 400 mg tablet salut selaput, tiap tablet mengandung zat aktif ibuprofen dalam bentuk garam L-arginine yang setara dengan 400 mg ibuprofen.
SPEDIFEN 400 mg tablet salut selaput juga mengandung: Sodium hydrogen carbonat, cropovidone, magnesium stearate, Hypermellose, sukrosa, Titanium dioxide dan Macrogol 4000.

1 box, 5 blister @ 6 Tablet salut selaput
No Reg : DKI1074300417A1

HARUS DENGAN RESEP DOKTER

Diproduksi oleh :
Zambon S.p.A.
Vicenza – Italy

Diimport oleh :
PT. Tunggal Idaman Abdi
Jakarta – Indonesia

Dipasarkan oleh :
PT Zambon Indonesia
Jakarta - Indonesia

DISETUJUI OLEH BPOM: 22/04/2026 ID: EREG10015512600022