BRUFEN 400 mg
Ibuprofen

NAME OF THE MEDICINAL PRODUCT
Ibuprofen 400 mg film-coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Ibuprofen 400 mg film-coated tablets
One tablet contains 400 mg ibuprofen.
Excipient with known effect: Lactose monohydrate

All formulations:
<For the full list of excipients, see section 6.1>

PHARMACEUTICAL FORM
Ibuprofen 400 film-coated tablet
Film-coated tablet
White, oval tablet

CLINICAL PARTICULARS

Therapeutic indications
Due to its analgesic and anti-inflammatory effects, ibuprofen is used to relief symptoms of rheumatic condition of bones, joints and non-joints. It is also used to relief symptoms due to traumatic conditions of muscles and bones/joints (musculoskeletal injuries).

Due to its analgesic effects, ibuprofen is used to relief mild to moderate pain such as primary dysmenorrheal (menstruation pain), dental pain or pain in dental extraction, post operative pain, and headache.

Posology and method of administration
Adults

1. For analgesic and anti-inflammatory use (rheumatic conditions of bones, joints and non-joints, muscle and bone/joint injuries):
Recommended dose is 3 to 4 times of 400 mg a day.
Dose at start is recommended to use a minimum effective dose 400 mg 3 times a day.

2. For analgesic use:
The recommended dose is 200 mg to 400 mg, 3 to 4 times a day.

Pediatric population

Brufen 400 mg tablets are not recommended for children.

Contraindications

- Brufen is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.
- Brufen should not be used in patients who have previously shown hypersensitivity reactions (e.g. asthma, urticaria, angioedema or rhinitis) after taking ibuprofen,aspirin or other NSAIDs.
- Brufen is also contraindicated in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Brufen should not be used inpatients with active, or history of, recurrent peptic ulcer or gastrointestinal haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Brufen should not be given to patients with conditions involving an increased tendency to bleeding.
- Last trimester in pregnancy.
- Severe heart failure (NYHA Class IV), hepatic failure and renal failure

Special warnings and precautions for use

General

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (*see section 4.2 - Posology and method of administration, and GI and cardiovascular risks below)*

On prolonged use of any painkillers, headache may occur that must not be treated with increased doses of the medicinal product.

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Information related to excipients:

Ibuprofen 400 mg film-coated tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Elderly population

Elderly patients have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal.

- **Gastrointestinal Bleeding, Ulceration and Perforation**

Ibuprofen should be given with care to patients with a history of peptic ulceration and other gastrointestinal disease since their conditions may be exacerbated *(see section 4.3)*

Gastrointestinal bleeding, ulceration or perforation has been reported with all NSAIDs at any time during treatment. These adverse can be fatal and may occur with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing ibuprofen doses in patients with a history of ulcers, particularly if complicated with hemorrhage or perforation, and in 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, as well as patients requiring concomitant low dose acetylsalicylic acid/aspirin, or for other drugs likely to increase gastrointestinal risk *(see section 4.5)*.

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

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

- Respiratory disorders

Caution is required if ibuprofen is administered to patients suffering from, or with a previous history of, bronchial asthma, chronic rhinitis, or allergic diseases since ibuprofen has been reported to cause bronchospasm, urticaria or angioedema in such patients.

- Cardiac, renal and hepatic impairment

Caution is required in patients with renal, hepatic or cardiac impairment since the use of NSAIDs may result in deterioration of renal function. The habitual concomitant intake of similar painkillers further increases this risk. For patients with renal, hepatic or cardiac impairment, use the lowest effective dose, for the shortest possible duration and monitor renal function especially in long-term treated patients *(see section 4.3 - contraindications)*.

- Cardiovascular and cerebrovascular effects

Ibuprofen should be given with care to patients with a history of heart failure or hypertension since edema has been reported in association with ibuprofen administration.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2,400 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. ≤ 1,200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischemic 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 longer-term treatment of patients with risk factor for cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, 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 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.

- Dermatological effects

Severe cutaneous adverse reactions (SCARs).

Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in connection with the use of Ibuprofen *(see section Undesirable effects)*. **Most of these reaction** occurred within the first month of treatment.If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Ibuprofen in case of varicella.

- Renal effects

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydrated. There is a risk of renal impairment especially in dehydrated children, adolescents, and the elderly.
As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may cause renal failure.
Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE inhibitors and the elderly. Discontinuation of NSAIDs therapy is usually followed by recovery to the pretreatment state.

Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

- Hematological effects

Ibuprofen, like other NSAIDs, can inhibit platelet aggregation and prolong bleeding time in normal subjects.

- Aseptic meningitis

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

Masking of symptoms of underlying infections
Ibuprofen 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 ibuprofen is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Interaction with other medicinal products and other forms of interaction
Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients:

Concomitant use of ibuprofen with:	**Possible effects**
Other NSAIDs including cyclooxygenase-2 selective inhibitors	Concomitants use with other NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the potential for additive effects *(see section 4.4)*
Cardiac glycoside	NSAIDs may exacerbate heart failure, reduce glomerular filtration rate and increased plasma cardiac glycoside.
Corticosteroids	Increased risk of gastrointestinal ulceration or bleeding with NSAIDs.
Anti-coagulants	NSAIDs may enhance the effects of anti-coagulants, such as warfarin.
Anti-platelet agents and Selective Serotonin Reuptake Inhibitors (SRRIs)	Increased risk of gastrointestinal bleeding with NSAIDs.
Acetylsalicylic acid/aspirin	As with other products containing NSAIDs, concomitant administration of ibuprofen and acetylsalicylic acid/aspirin 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/aspirin 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 section 5.1*)
Lithium	NSAIDs may decrease elimination of lithium.
Anti-hypertensives, beta blockers and diuretics	NSAIDs may reduce the effect of anti-hypertensives, such as ACE inhibitors, angiotensin II receptor antagonists, betablockers and diuretics. Diuretics can also increase the risk of nephrotoxicity of NSAIDs.
Methotrexate	NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate
Cyclosporine	Increased risk of nephrotoxicity with NSAIDs.
Tacrolimus	Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Zidovudine	Increased risk of hematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of hemarthrosis and hematoma in HIV (+) hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen
Quinolone antibiotics	Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Aminoglycosides	NSAIDs may decrease the excretion of aminoglycosides.
Herbal extracts	Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.
Mifepristone	NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Fertility, Pregnancy and Lactation

While no teratogenic effects have been demonstrated in animal toxicology studies, the use of ibuprofen during pregnancy should be avoided. Congenital abnormalities have been reported in association with ibuprofen administration in man, however these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAID on the fetal cardiovascular system (closure of ductus arterius) use in late pregnancy should be avoided.

Labor and delivery

Administration of ibuprofen is not recommended during labor and delivery. The onset of labor may be delayed and the duration increased with a greater bleeding tendency in both mother and child.

Breastfeeding

In the limited studies so far available, ibuprofen appears in the breast milk in very low concentrations. Ibuprofen is not recommended for use in nursing mothers.

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. In animals, the administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation losses and embryo/fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, ibuprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first or second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

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

At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the neonate to the following:

- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
- Inhibition of uterine contractions, which may result in delayed or prolonged labor.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy

Undesirable Effects

The pattern of adverse events reported for ibuprofen is similar to that of other NSAIDs.

- **Gastrointestinal disorders**

  The most commonly observed adverse events are gastrointestinal in nature. Nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, gastrointestinal hemorrhage and exacerbation of colitis and Crohn's disease *(see section 4.3)* have been reported following ibuprofen administration. Less frequently, gastritis, duodenal ulcer and gastric ulcer and gastrointestinal perforation have been observed.

  A transient sensation of burning in the mouth or throat may occur with Ibuprofen granules.

- **Immune system disorders**

  Hypersensitivity reaction has been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, very rarely, erythema multiforme, bullous dermatoses (including Stevens-Johnson syndrome and toxic epidermal necrolysis).

- **Infections and infestations**

  Exacerbation of skin infection-related inflammations (e.g. development of necrotizing fasciitis) coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of Ibuprofen the patient is therefore recommended to go to a doctor without delay.

- **Skin and subcutaneous tissue disorders**

  In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations")

- **Cardiac and vascular disorders**

  Clinical studies data suggest that use of ibuprofen (particularly at a high doses of 2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (*for example myocardial infarction or stroke*, (*see section 4.4 - Special warnings and precautions for use).*

The following adverse reactions possibly related to ibuprofen ad display by MedDRA frequency convention and system organ classification. Frequency groupings are classified according to the subsequent conventions: 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).

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Rhinitis
	Rare	Meningitis aseptic (*see section 4.4*)
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anemia and hemolytic anemia
Immune system disorder	Uncommon	Hypersensitivity
	Rare	Anaphylactic reaction
Psychiatric disorders	Uncommon	Insomnia, anxiety
	Rare	Depression, confusional state
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Paresthesia, somnolence
	Rare	Optic neuritis
Eye disorders	Uncommon	Visual impairment
	Rare	Toxic optic neuropathy
Ear and labyrinth disorders	Uncommon	Hearing impaired, tinnitus, vertigo
Respiratory, thoracic and mediastinal disorders	Uncommon	Asthma, bronchospasm, dyspnea
Gastrointestinal disorders	Common	Dyspepsia, diarrhea, nausea, vomiting, abdominal pain, flatulence, constipation, melena, hematemesis, gastrointestinal hemorrhage
	Uncommon	Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation
	Very rare	Pancreatitis
	Not known	Colitis and Chron's disease
Hepatobiliary disorders	Uncommon	Hepatitis, jaundice, hepatic function abnormal
	Very rare	Hepatic failure
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	urticaria, pruritus, purpura, angioedema
	Very rare	Severe cutaneous adverse

System Organ Class	Frequency	Adverse reaction
		reactions (SCARs) including (e.g. Erythema multiforme, exfoliative dermatitis, bullous reaction including Steven-Johnson syndrome, and toxic epidermal necrolysis)
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP), photosensitivity reactions
Metabolism and Nutrition Disorders	Not known	Decreased appetite hypokalaemia*
Renal and urinary disorders	Uncommon	Nephrotoxicity in various forms, e.g. tubulointerstitial nephritis, nephrotic syndrome and renal failure
	Very rare	Acute renal failure
	Not known	Ureteric colic, dysuria Renal tubular acidosis*
General disorders and administration site conditions	Common	Fatigue
	Rare	Edema
Cardiac disorders	Very rare	Cardiac failure, myocardial infarction (*also see section 4.4*)
	Not Known	Kounis Syndrome
Vascular disorders	Very rare	Hypertension

*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.

Reporting of suspected adverse reactions

Reporting suspected adverse reaction after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system email:

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

Website: https://e-meso.pom.go.id

Overdose

Symptoms

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours.

The most frequently reported symptoms of overdose include nausea, vomiting, abdominal pain, lethargy and drowsiness. Central Nervous System (CNS) effect include headache, tinnitus, dizziness, convulsion, loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnea, diarrhoea and depression of the CNS and respiratory system have also been rarely reported. Cardiovascular toxicity, including hypotension, bradycardia and tachycardia, has been reported. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors.

Disorientation, excitation, fainting and cardiovascular toxicity, including hypotension, bradycardia and tachycardia have been reported. In cases of significant overdose, renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other drugs are being taken.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section Special warnings and precautions for use and section Undesirable effect).

Treatment

There is no specific antidote to ibuprofen. Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. If necessary, serum electrolyte balance should be corrected.

Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Ibuprofen is a propionic acid derivative non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and anti-pyretic effects. The drug's therapeutic effects are thought to result from its inhibitory effect on the enzyme cyclooxygenase, which results in a marked reduction in prostaglandin synthesis.

Experimental data suggest that ibuprofen may competitively the effect of low dose acetylsalicylic acid/aspirin on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate release acetylsalicylic acid/aspirin dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid/aspirin cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (*see section 4.5*).

Pharmacokinetic Properties

Absorption

Ibuprofen is rapidly absorbed from the gastrointestinal tract with a bioavailability of 80-90%. Peak serum concentrations occur one to two hours after administration. Studies including a standard meal show that food does not markedly affect total bioavailability.

The elimination half-life is approximately two hours. Ibuprofen is metabolized in the liver into two inactive metabolites and the kidney excretes these, together with unchanged ibuprofen, either as such or as conjugates. Excretion by the kidney is both rapid and complete.

Ibuprofen is extensively bound to plasma proteins.

Preclinical Safety Data

There are no preclinical data of relevance for the safety assessments, apart from what has already been taken into account in this package insert.

PHARMACEUTICAL PARTICULARS

List of excipients

Cellulose microcrystalline
Croscarmellose sodium
Lactose monohydrate
Silicon laurilsulfate
Magnesium stearate
Film coating

Shelf life
2 years

Special precaution for storage
Do not store above 30^{O}C

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

PRESENTATION
Box of 10 blisters @ 10 film-coated tablets
Reg. No.: DKL0400202917B1
Box of 3 blisters @ 10 film-coated tablets
Reg. No.: DKL0400202917B1

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Jl Raya Jakarta – Bogor Km 37, Cimanggis
Depok 16415, Indonesia

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