BUNAFEN RTU
IBUPROFEN
Infusion 4 mg/mL

NAME OF THE MEDICINAL PRODUCT

Bunafen RTU Infusion 4 mg/mL

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 4 mg of Ibuprofen.
Each 100 ml bottle contains 400 mg of Ibuprofen.

Excipient with known effect:
Each ml of solution contains 3.71 mg of sodium.
Each 100 ml bottle contains 371 mg of sodium.

For the full list of excipients, see section 'Excipients'

PHARMACEUTICAL FORM

Solution for infusion.
Clear and colourless solution for infusion.

pH: 7.2-8.0
Osmolality: 270-330 mOsmol/Kg

Warning : Risk of Serious Cardiovascular and Gastrointestinal Events

Cardiovascular Risk:
- Non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of serious cardiovascular (CV) 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 (see Warning and precautions).
- Ibuprofen is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see contraindications and warnings and precautions).

Gastrointestinal Risk:
- NSAIDs increase the risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach 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 (see warning and precautions).

CLINICAL PARTICULARS

Therapeutic indications

Ibuprofen is indicated in adults for the management of acute moderate to severe pain as an adjunct to intravenous opioid analgesics where an intravenous route of administration is considered clinically necessary.

Posology and method of administration

Posology

Administer 400 mg to 800 mg intravenously every 6 hours as necessary. Infusion time must be at least 30 minutes. The highest recommended dose is 2400 mg daily. Do not exceed 3200 mg. Similarly, going beyond 24 hours must be justified based on benefits over risk assessment.

Visually inspection injection for particulate matter and discolouration prior to administration, wherever solution and container permit. If visibly opaque particles, discolouration or other foreign particulates are observed, the solution should not be used. It is a sterile solution for single use and contains no antimicrobial preservative.

Infusion time is 30 minutes.

Injection should be used in one patient on one occasion only. It contains no antimicrobial preservative. Unused solution should be discarded.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section Excipients.
- A history of bronchospasm, asthma, rhinitis, angioedema or urticaria associated with taking acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory drugs (NSAIDs).
- Conditions involving an increased tendency to or active bleeding such as thrombocytopenia.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Cerebrovascular or other active bleeding.
- Severe hepatic or renal insufficiency.
- Severe heart failure (NYHA Class IV).
- Severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).
- Pregnancy, in the last trimester (see section Pregnancy, Fertility and Lactation).
- Ibuprofen is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) Surgery

Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest possible time necessary to control symptoms (see section Undesirable effects).
Concomitant use of Ibuprofen with NSAIDs, including cyclooxygenase-2 selective inhibitors (Coxib), should be avoided.
The frequency of the adverse reactions to NSAIDs is increased in elderly patients, especially gastrointestinal bleeding and perforation which may be fatal (see section Undesirable effects).

Gastrointestinal risks
NSAID including Ibuprofen, can cause serious GI adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These

serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse events on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAID occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short term therapy is not without risk.
Prescribe NSAIDs, including Ibuprofen, with extreme caution in those with a prior history of ulcer disease or GI bleeding. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to treated patients neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most reports of spontaneous fatal GI events are in elderly or debilitated patients, and therefore special care should be taken in treating this population.
To minimize the potential risk for an adverse GI event in patients treated with an NSAID, use the lowest effective dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Cardiovascular and cerebrovascular effects
Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk.
To minimize the potential risk for an adverse CV event in patients treated with an NSAID, use the lowest effective dose for the shortest duration possible. Physician and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.
Two large, controlled clinical trials of COX-2 selective NSAID for the treatment of pain in the first 10 – 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke.
There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious gastrointestinal (GI) events.

Serious Skin Reaction
NSAIDS, including ibuprofen, can cause serious skin adverse reaction such as exfoliative dermatitis, stevens-johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Informs patients about the signs and symptoms of serious skin manifestation.

Hepatic Effects
Borderline elevation of one or more liver test may occur in up to 15% of patients taking NSAIDs, including Ibuprofen. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions have been reported, including jaundice, fulminant hepatitis, liver necrosis and hepatic failure, some with fatal outcomes.
A patient with symptoms and/or signs suggesting liver dysfunction, or with abnormal liver test values, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with Ibuprofen. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestation occur (eg., eosinophilia, rash, etc) Ibuprofen should be discontinued.

Renal effects
Use caution when initiating treatment with Ibuprofen in patients with considerable dehydration. Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury, 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 NSAID may cause a dose dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate over renal decompensation.
Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics or ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state, no information is available from controlled clinical studies regarding the use of Ibuprofen in patients with advanced renal disease. If Ibuprofen therapy must be initiated in patients with advanced renal disease, closely monitor the patient's renal function.

Anaphylactoid reactions
As standard practice during intravenous infusion, close patient monitoring is recommended, especially at the beginning of the infusion to detect any anaphylactic reaction caused by the active substance or the excipients.
Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are very rarely observed. At the first signs of a hypersensitivity reaction following the administration of Ibuprofen, therapy must be stopped and symptomatic treatment must be established. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.
Ibuprofen is contraindicated in patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDS [See Contraindication].

Pre-existing Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity between aspirin and NSAIDs has been reported in such aspirin-sensitive patients, including bronchospasm. Ibuprofen contraindicated in patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

Haematological effects
Ibuprofen may temporarily inhibit the blood-platelet function (thrombocyte aggregation), increasing the bleeding time and the risk of haemorrhage.
Ibuprofen should only be used with particular caution in patients receiving ASA to inhibit platelet aggregation (see sections Interaction with other medicinal products and other forms of interaction and Pharmacodynamic properties).
Patients with coagulation disorders or those undergoing surgery should therefore be monitored. Special medical vigilance is required for use in patients immediately after undergoing major surgery.
During prolonged Ibuprofen administration, regular checking of liver values, kidney function, and blood counts, is required.
Ibuprofen should be used only after strict assessment of the benefit / risk balance in patients with congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria).

Anaemia may occur in patients receiving NSAIDs, including Ibuprofen. This may be due to fluid retention, occur or gross GI blood loss, or an incompletely described effect on erythropoiesis. In patients on long-term treatment with NSAIDs, including Ibuprofen, check haemoglobin or haematocrit if they exhibit any signs or symptoms of anaemia or blood loss. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effects on platelet function are less severe quantitatively, of shorter duration, and reversible. Carefully monitor patients who may be adversely affected by alterations in platelet function, such as those with

coagulation disorders or patients receiving anticoagulants.

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.

Caution is required in patients with certain conditions, which may be made worse:
- In patients who react allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of this medicinal product.
- In patients who suffer from hay fever, nasal polyps or chronic obstructive respiratory disorders as an increased risk exists for them of allergic reaction occurring. These may present as asthma attacks (so-called analgesic asthma), Quincke´s oedema or urticaria.

Aseptic meningitis
Some cases of aseptic meningitis have been reported with the use of Ibuprofen in patients with systemic lupus erythematosus (SLE). Although it is more likely to occur in patients with SLE and related connective tissue diseases, it has also been reported in some patients who do not have any underlying chronic disease. Therefore, this should be taken into account when administering this treatment (see section Undesirable effects).

Masking of symptoms of underlying infections
Ibuprofen can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worse 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.
NSAIDs can mask the symptoms of concurrent infections.

Interference with analytical tests
- Bleeding time (may be extended for a day after discontinuation of therapy)
- Blood glucose concentration (may decrease)
- Creatinine clearance (may decrease)
- Haematocrit or haemoglobin (may decrease)
- Blood levels of urea nitrogen and serum creatinine and potassium (may increase)
- Liver function tests: increased transaminases values

Ophthalmological effects
Blurred or diminished vision, scotomata, and changes in colour vision have been reported with oral Ibuprofen. Ibuprofen should be discontinued if the patient develops such complaints, and the patient should be referred for an ophthalmologic examination that includes central visual fields and colour vision testing.

Hypertension
NSAID, including Ibuprofen, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Use NSAIDs, including Ibuprofen, with caution in patients with hypertension. Monitor blood pressure closely during the initiation of NSAID treatment and throughout the course of therapy. Patients taking ACE inhibitors, thiazides, or loop diuretics may have impaired response to these therapies when taking NSAIDs.

Congestive heart failure and edema
Fluid retention and edema have been observed in some patients taking NSAIDs. Use Ibuprofen with caution in patients with fluid retention or heart failure.

Pregnancy
Starting at 30 weeks gestation, Ibuprofen and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the foetus may occur [see Pregnancy, fertility, and Lactation]

Masking inflammation and fever
The pharmacological activity of Ibuprofen in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed non-infectious, painful conditions.

Monitoring
Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have CBC chemistry profiles checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestation occur (e.g. eosinophilia, rash), or abnormal liver test persist or worsen, discontinue Ibuprofen.

Others
Prolonged use of painkillers may cause headache that must not be treated with increased doses of the medicinal product.
Exceptionally, varicella can cause 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.

Precautions regarding excipients
This medicinal product contains 371 mg sodium per bottle, equivalent to 18.6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interaction with other medicinal products and other forms of interaction

Other NSAIDs, including COX-2 inhibitors and salicylates
As a result of synergist effects, the concurrent administration of two or more NSAIDs may increase the risk of gastrointestinal ulcers and bleeding. Co-administration of Ibuprofen with other NSAIDs should therefore be avoided (see section Special warnings and precautions for use).
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 section Pharmacodynamic properties).

Lithium
Ibuprofen should not be avoided in patients taking lithium as NSAIDS have produced elevations of plasma lithium levels and a reduction in renal lithium clearance.

Digoxin and Other Cardiac Glycosides
The concomitant use of Ibuprofen with digoxin and other cardiac glycosides preparations may exacerbate cardiac failure, reduce glomerular filtration rate, and increase serum level of digoxin and other glycosides. Monitoring of serum digoxin is recommended.

Phenytoin
The concomitant use of Ibuprofen with phenytoin preparations may increase serum level of phenytoin. A check of serum-phenytoin levels is not as a rule required on correct use of Ibuprofen (no more than 3 days).

Antihypertensive (diuretics, ACE inhibitors, beta-receptor blocking medicinal products and angiotensin-II antagonists)
Diuretics and ACE-inhibitors may increase the nephrotoxicity of NSAIDs. NSAIDs can reduce the effect of diuretics and other antihypertensive medicinal products, including ACE inhibitors and beta-blockers with possible loss of blood pressure control and can attenuate the natriuretic effects of thiazide diuretics and furosemide. This response has been attribute to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, observes patients closely for signs of renal failure, as well to assure diuretic efficacy. In patients with reduced kidney function (e.g. dehydrated patients or elderly patients with reduced kidney function) the concomitant use of an ACE inhibitor and angiotensin-II antagonists with a cyclo-oxygenase-inhibiting medicinal product can lead to further impairment of kidney function, through to acute renal failure. This is usually reversible. Such combinations should therefore, only be used with caution, especially in elderly patients. Patients have to be instructed to drink sufficient liquid and periodic monitoring of kidney values should be considered for the time immediately after the start of concomitant therapy. The concomitant administration of Ibuprofen with ACE-inhibitors may lead to hyperkalaemia.

Potassium sparing diuretics
Concomitant use may cause hyperkalaemia (check of serum potassium is recommended).

Captopril
Experimental studies indicate that Ibuprofen counteracts the effect of captopril of increased sodium excretion.

Corticosteroids
Increased risk of gastrointestinal ulceration or bleeding (see section Special warnings and precautions for use).

Anti-platelet medicinal products (e.g. clopidogrel and ticlopidine) and selective serotonin reuptake inhibitors (SSRIs)
Increased risk of gastrointestinal bleeding (see section Special warnings and precautions for use). NSAIDs should not be combined with ticlopidine due to the risk of an additive effect in the inhibition of platelet function.

Methotrexate
NSAIDs inhibit the tubular secretion of methotrexate and certain metabolic interactions may occur resulting in decreased clearance of methotrexate. The administration of Ibuprofen within 24 hours before or after administration of methotrexate may lead to an elevated concentration of methotrexate and an increase in its toxic effect. Therefore, concomitant use of NSAIDs and high doses of methotrexate should be avoided. Also, the potential risk of interactions in low dose treatment with methotrexate should be considered, especially in patients with impaired renal function. In combined treatment, renal function should be monitored.

Ciclosporin
The risk of a kidney-damage by ciclosporin is increased by the concomitant administration of certain NSAIDs. This effect cannot be ruled out for a combination of cyclosporin and Ibuprofen either.

Anti-coagulants
NSAIDs may enhance the effect of anti-coagulants, such as warfarin (see section Special warnings and precautions for use). In case of simultaneous treatment, monitoring of the coagulation state is

recommended.
The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that the user of both drugs together have a higher risk of serious GI bleeding than users of either drug alone.

Sulphonylureas
NSAIDs can increase the hypoglycaemic effect of sulphonylureas. In the case of simultaneous treatment, monitoring of blood glucose levels is recommended.

Tacrolimus
Elevated risk of nephrotoxicity.

Zidovudine
There is evidence of an increased risk of hemarthrosis and hematomas in HIV positive haemophilia patients receiving concurrent treatment with zidovudine and Ibuprofen. There may be an increased risk of haematoxicity during concomitant use of zidovudine and NSAIDs. Blood counts 1-2 weeks after starting concomitant use are recommended.

Probenecid and sulfinpyrazone
Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of 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.

CYP2C9 Inhibitors
Concomitant administration of Ibuprofen with CYP2C9 inhibitors may increase the exposure to Ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-Ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the Ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose Ibuprofen is administered with either voriconazole or fluconazole.

Mifepristone
If NSAIDs are used within 8-12 days after the mifepristone administration, they may decrease the effect of mifepristone.

Alcohol
The use of Ibuprofen in individuals with chronic alcohol consumption (14-20 drinks/week or more) should be avoided due to increased risk of significant GI adverse effects, including bleeding.

Aminoglycosides
NSAIDs may decrease the excretion of aminoglycosides and increase their toxicity.

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

H-2 Antagonist
In studies of human volunteers, co-administration of Cimetidine or Ranitidine with Ibuprofen had no substantive effect on Ibuprofen serum concentration.

Pregnancy, Fertility and Lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy.
In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal 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 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 ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

Ibuprofen is contraindicated for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition.

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

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

The mother and the neonate, at the end of the pregnancy, to:
- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
- Inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Ibuprofen use is contraindicated during the third trimester of pregnancy (See section Contraindications).

Breastfeeding
Ibuprofen and its metabolites pass only in low concentrations into breast milk. Because of the potential for serious adverse reactions in nursing infant from ibuprofen, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

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

Effects on ability to drive and use machines

Ibuprofen, in single or short-term use has no or negligible influence on the ability to drive and use machines. However, the occurrence of relevant undesirable effects such as fatigue and vertigo can

impair reactivity and the ability to drive a vehicle and/or use machines may be reduced. This particularly applies when combined with alcohol.

Undesirable effects

The following frequencies are taken as a basis when evaluating undesirable effects:
Very common: ≥ 1/10 Common: ≥1/100 to< 1/10 Uncommon: ≥1/1,000 to< 1/100 Rare: ≥1/10,000 to< 1/1,000 Very rare: <1/10,000
Not known: frequency cannot be estimated from the available data.

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly may occur (see section Special warnings and precautions for use). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed. Particularly the risk of gastrointestinal bleeding occurring is dependent on the dose range and the duration of use.
Very rarely severe hypersensitivity reactions (including infusion site reactions, anaphylactic shock) and serious cutaneous adverse reactions such as bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), erythema multiforme and alopecia have been reported.

Exacerbation of infection-related inflammation (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. This is possibly associated with the mechanism of action of the NSAIDs.
Photosensitivity, allergic vasculitis and in exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see section Special warnings and precautions for use).

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

The following serious adverse reaction are discussed elsewhere in the labelling:
- Cardiovascular thrombotic events [see Boxed warning and warning and precautions]
- Gastrointestinal effects [see Boxed warning and warning and precautions]
- Hepatic effects [see warning and precautions]
- Hypertension [see warning and precautions]
- Congestive heart [see warning and precautions]
- Renal effects [see warning and precautions]
- Anaphylactoid reaction [see warning and precautions]
- Serious skin reactions [see warning and precautions]

System organ class	**Adverse reaction**
Infections and infestations	Very rare: Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. This is possibly associated with the mechanism of action of the NSAIDs
	Cellulitis, urinary tract infection fungal, vulvovaginal mycotic infection
Blood and lymphatic system disorders	Very rare: Disturbances to blood formation (anaemia, agranulocytosis, leucopoenia, thrombocytopenia, and pancytopenia,). First symptoms are: fever, sore throat,

	superficial mouth wounds, influenza-like complaints, severe lassitude, nosebleeds and skin bleeding
Immune system disorders	Uncommon: Hypersensitivity reactions with skin rashes and itching, as well as asthma attacks (possibly with drop in blood pressure)
	Very rare: Systemic lupus erythematosus (SLE), severe hypersensitivity reactions, face oedema, swelling of the tongue, swelling of the internal larynx with constriction of the airways, difficulty breathing, palpitations, hypotension and life threatening shock)
Psychiatric disorders	Uncommon: Anxiety, restlessness
	Rare: Psychotic reactions, nervousness, irritability, confusion or disorientation and depression
Nervous System disorders	Very common: Fatigue or sleeplessness, headache, dizziness
	Uncommon: Insomnia, agitation, irritability or tiredness
	Very rare: Aseptic meningitis (stiff neck, headache, nausea, vomiting, fever or confusion) Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed
	Hypoesthesia, syncope, tremor
Eye disorders	Uncommon: Visual disturbances
	Rare: Reversible toxic amblyopia
Ear and labyrinth disorders	Common: Vertigo
	Uncommon: Tinnitus
	Rare: Hearing disorders
Cardiac disorders	Very rare: Palpitations, heart failure, myocardial infarction
	Not known: Kounis syndrome
Vascular disorders	Very rare: Arterial hypertension
	Deep vein thrombosis, hematoma, wound haemorrhage
Respiratory, thoracic and mediastinal disorders	Very rare: Asthma, bronchospasm, dyspnoea and wheezing
	Cough, dyspnoea, epistaxis, nasal congestion, pharyngeal oedema, pharyngolaryngeal pain, pulmonary embolism, pulmonary oedema, respiratory depression, respiratory failure, sleep apnoea syndrome, wheezing
Gastrointestinal disorders	Very common: Pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation and slight gastro-intestinal blood losses that may cause anaemia in exceptional cases
	Common: Gastrointestinal ulcers, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn´s disease
	Uncommon: Gastritis
	Rare: Oesophageal stenosis, exacerbation of diverticular disease, non-specific haemorrhagic colitis. If gastrointestinal bleeding occurs could cause anaemia and haematemesis
	Very rare: Oesophagitis, pancreatitis, formation of intestinal, diaphragm- like strictures
	Abdominal discomfort, abdominal pain upper, dry mouth, ileus, dyspepsia
Hepatobiliary disorders	Rare: Jaundice, hepatic dysfunction, hepatic damage, particularly in long-term therapy, acute hepatitis
	Not known: Hepatic insufficiency
Surgical and medical	Wound drainage

procedures	
Skin and subcutaneous tissue disorders	Common: Skin eruption
	Uncommon: Urticaria, pruritus, purpura (including allergic purpura), skin rash
	Very rare: Severe cutaneous adverse reactions (SCARs) (including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis), alopecia. Photosensitivity reactions and allergic vasculitis. In exceptional cases, severe skin infections and soft-tissue complications in varicella infection (see also "Infections and infestations").
	Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalised exanthematous pustulosis (AGEP)
	Cellulitis, decubitus ulcer, dermatitis allergic, hyperhidrosis, rash
Musculoskeletal and connective tissue disorders	Rare: Stiff neck
	Arthralgia, back pain, neck pain, pain extremity
Renal and urinary disorders	Uncommon: Reduced urinary excretion and formation of oedemas, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis that may be accompanied by acute renal insufficiency.
	Rare: Renal tissue damage (papillary necrosis), particularly in long- term therapy, increased serum uric acid concentration in the blood
	Hematuria, renal failure acute, urinary retention
Metabolism and nutrition disorders	Acidosis, hyperglycemia, hypoglycemia, hypomagnesemia, hyponatremia, hypokalemia
Investigations	Blood albumin decreased, blood creatinine increased, blood glucose increased, blood pressure increased, blood test abnormal, breath sound abnormal, hepatic enzyme increased, liver function test abnormal, oxygen saturation decreased, platelet count decreased, urine output decreased, hemoglobin decreased
Injury, poisoning and procedural complications	Anemia postoperative, postoperative wound infection, procedural pain, wound complication
General disorders and administration site conditions	Common: Pain and burning sensation in at the administration site
	Not known: Injection site reactions such as swelling, hematoma or bleeding.
	Chest pain, edema peripheral, inflammation, infusion site bruising, infusion site extravasation, infusion site irritation, multiorgan failure
Endocrine disorders	Adrenal insufficiency

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 pv.indonesia@fresenius-kabi. And/or through the national reporting system:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makananan (BPOM) RI
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Overdose

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

Symptoms
Central nervous system disturbances include headache, tinnitus, confusion, nystagmus, dizziness, light-headedness, unconsciousness convulsions (mainly in children) and ataxia, as well as abdominal pain, nausea and vomiting may occur as symptoms of an overdose. In addition, gastrointestinal bleeding as well of functional disturbances of the liver and kidneys are possible. Furthermore, hypotension, hyperkalaemia, hypothermia respiratory depression and cyanosis occur.

In serious poisoning metabolic acidosis may occur.

Treatment
Treatment is symptomatic and there is no specific antidote.
The therapeutic possibilities for treatment of intoxication are dictated by the extent, level and clinical symptoms according to the common intensive care practices.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: *Anti-inflammatory and antirheumatic products, non-steroids. Propionic acid derivatives*.
ATC code: *M01AE01*

Mechanism of action
Ibuprofen is a non-steroidal anti-inflammatory drug that, in conventional animal-experimental inflammation models, has proven to be effective, probably through prostaglandin synthesis inhibition. In humans, Ibuprofen has an antipyretic effect, reduces inflammatory-related pain and swelling.
Furthermore, Ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation.

Special populations

Paediatric use
Safety and efficacy of Ibuprofen for the treatment of pain has not been established in paediatric patients below the age of 18 years.

Geriatric use
Clinical studies of Ibuprofen did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Dose selection for an elderly

patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients are at increased risk for serious GI Adverse events.

PHARMACEUTICAL PARTICULARS

Excipients

Disodium phosphate dodecahydrate
Hydrochloric acid (pH adjustment)
Sodium chloride
Sodium dihydrogen phosphate dihydrate
Sodium hydroxide (pH adjustment)
Water for injections

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelflife

24 months.
From a microbiological point of view, the product should be used immediately after opening. Otherwise, the in-use storage time and conditions prior to use are in the responsibility of the user.

Special precautions for storage

Store below 30°C
Do not freeze. Keep the bottle in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section Special precautions for storage.

Nature and contents of container

The solution for infusion is presented in 100 ml LDPE bottles in pack of 1 bottle.

No. Reg : DKI xxxxxxxxxxxx

Special precautions for disposal

Ibuprofen is indicated for use as single dose; any unused solution should be discarded. Before administration, the solution should be visually inspected to ensure it is clear and colourless solution. It should not be used if any visible particles are observed.

This medicinal product poses a risk to the environment.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufactured by:
Fresenius Kabi Polska Sp. z o.o.
ul. Sienkiewicza 25
PL - 99-300 Kutno
Poland

On behalf of:
Fresenius Kabi Deutschland GmbH
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Imported by:
PT. Fresenius Kabi Combiphar
Bandung Barat – Indonesia

HARUS DENGAN RESEP DOKTER

Leaflet kemasan: Informasi Produk untuk Pasien
BUNAFEN RTU 4 mg/ml
Larutan untuk Infus

Baca keseluruhan isi leaflet ini dengan seksama sebelum Anda diberikan obat ini karena ini mengandung informasi penting untuk Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Jika Anda mengalami efek samping, termasuk yang tidak tercantum dalam leaflet ini, konsultasikan dengan dokter, apoteker, atau perawat. Lihat bagian 4.

Apa yang tercantum di leaflet ini?

1. Apa itu Ibuprofen dan apa kegunaannya

Bunafen mengandung Ibuprofen yang termasuk dalam kelompok obat yang disebut "obat anti-inflamasi nonsteroid" atau (AINS).
Obat ini digunakan untuk mengatasi nyeri akut sedang hingga berat sebagai tambahan untuk analgesik opioid intravena di mana rute pemberian intravena dianggap perlu.

Peringatan: Dapat Terjadi Risiko Kejadian Kardiovaskular dan Saluran Pencernaan yang Serius

Risiko Kardiovaskular:
• Obat antiinflamasi nonsteroid (NSAID) dapat meningkatkan risiko kejadian trombotik kardiovaskular (CV) yang serius, infark miokard, dan stroke, yang dapat berakibat fatal. Risiko ini dapat meningkat seiring dengan bertambahnya durasi penggunaan. Pasien dengan penyakit kardiovaskular atau faktor risiko untuk penyakit kardiovaskular mungkin berisiko lebih besar (lihat bagian 'Peringatan dan Perhatian').
• Ibuprofen dikontraindikasikan untuk pengobatan nyeri peri-operatif pada pembedahan *Coronary artery bypass grafting* (CABG) (lihat bagian 'Kontraindikasi', 'Peringatan dan Perhatian').

Risiko Gastrointestinal:
• NSAID meningkatkan risiko kejadian tidak diinginkan gastrointestinal (GI) yang serius termasuk perdarahan, ulserasi, dan perforasi lambung atau usus, yang dapat berakibat fatal. Hal ini dapat terjadi sewaktu-waktu selama penggunaan dan tanpa gejala peringatan. Pasien lanjut usia lebih berisiko mengalami kejadian hal ini (lihat 'Peringatan dan Perhatian').

2. Apa yang perlu Anda ketahui sebelum Anda diberikan Bunafen

Bunafen tidak boleh diberikan:

- Jika Anda alergi terhadap Ibuprofen atau bahan lain dari obat ini (tercantum pada bagian 6).
- Jika Anda pernah menderita sesak napas, pernah menderita asma, ruam kulit, rinitis, atau pembengkakan wajah, saat sebelumnya mengonsumsi Ibuprofen, asam asetilsalisilat, atau obat penghilang rasa sakit lain yang sejenis (AINS).
- Jika Anda memiliki kondisi yang berhubungan dengan peningkatan kecenderungan atau perdarahan aktif.
- Jika Anda menderita atau memiliki riwayat tukak lambung atau perdarahan berulang (dua episode atau lebih).
- Jika Anda pernah mengalami perdarahan atau kebocoran di lambung atau usus saat mengonsumsi AINS.
- Jika Anda menderita perdarahan di otak (perdarahan serebrovaskular) atau perdarahan aktif lainnya.
- Jika Anda menderita masalah ginjal, hati, atau jantung yang parah.
- Jika Anda menderita dehidrasi berat (disebabkan oleh muntah, diare, atau asupan cairan yang tidak mencukupi).
- Jika Anda berada di trimester terakhir kehamilan.
- Jika Anda memiliki riwayat operasi *bypass* jantung (*Heart Bypass Surgey*). Hal ini dapat meningkatkan serangan jantung atau stroke.

Peringatan dan perhatian

Bicarakan kepada dokter, apoteker, atau perawat sebelum menggunakan Ibuprofen

Obat antiinflamasi/penghilang rasa sakit seperti Ibuprofen dapat dikaitkan dengan peningkatan kecil risiko serangan jantung atau *stroke*, terutama bila digunakan dalam dosis tinggi. Dosis atau durasi pengobatan yang direkomendasikan tidak boleh dilampaui.

Tanda-tanda reaksi alergi terhadap obat ini, termasuk masalah pernafasan, pembengkakan pada daerah wajah dan leher (angioedema), nyeri dada telah dilaporkan pada penggunaan Ibuprofen. Hentikan segera Bunafen dan segera hubungi dokter atau kontak darurat medis jika Anda menyadari adanya tanda-tanda ini.

Diskusikan pengobatan Anda dengan dokter sebelum menerima Ibuprofen:

- Jika Anda memiliki masalah jantung termasuk gagal jantung, angina pektoris (nyeri dada), atau jika Anda pernah mengalami serangan jantung, operasi *bypass*, penyakit arteri perifer (sirkulasi yang buruk di kaki karena penyempitan atau penyumbatan arteri), atau jenis *stroke* lainnya (termasuk '*mini-stroke*' atau serangan iskemik transien "TIA").
- Jika Anda memiliki tekanan darah tinggi, diabetes, kolesterol tinggi, memiliki riwayat keluarga terkait penyakit jantung atau *stroke*, atau jika Anda seorang perokok.
- Jika Anda baru saja menjalani operasi besar.
- Jika Anda pernah atau mengalami tukak, perdarahan atau perforasi lambung atau duodenum. Dalam kasus ini, dokter Anda akan mempertimbangkan untuk meresepkan obat pelindung mukosa lambung.
- Jika Anda menderita asma atau gangguan pernapasan lainnya, termasuk pasien asma yang memiliki riwayat sensitif terhadap Aspirin
- Jika Anda memiliki infeksi – silakan lihat judul “Infeksi” di bawah ini.
- Jika Anda memiliki penyakit ginjal atau penyakit hati, berusia lebih dari 60 tahun atau menggunakan Ibuprofen jangka panjang, dokter Anda mungkin perlu melakukan pemeriksaan secara teratur. Dokter Anda akan memberi tahu Anda frekuensi pemeriksaan ini.
- Jika Anda mengalami dehidrasi, misalnya karena diare, minum banyak cairan dan segera hubungi dokter karena Ibuprofen dalam hal ini dapat menyebabkan gagal ginjal akibat dehidrasi.

- Reaksi kulit yang serius termasuk dermatitis eksfoliatif, sindrom Stevens-Johnson, nekrolisis epidermal toksik yang bisa berakibat fatal. Efek yang serius ini bisa terjadi tanpa ada gejala. Berhenti menggunakan Bunafen dan segera mencari bantuan medis, jika Anda menyadari adanya gejala terkait reaksi kulit serius seperti dideskripsikan pada bagian 4.
- Jika Anda menderita penyakit Crohn atau kolitis ulseratif karena Ibuprofen dapat memperburuk kondisi ini.
- Jika Anda melihat ada luka, pembengkakan, atau kemerahan pada kulit, kesulitan bernapas (sesak napas), segera hentikan pengobatan dan hubungi dokter atau perawat Anda.
- Jika Anda memiliki varicella, karena komplikasi dapat terjadi.
- Jika Anda memiliki kelainan bawaan metabolisme porfirin (misalnya porfiria intermiten akut).
- Jika Anda menderita rhinitis alergi, polip hidung, atau penyakit paru obstruktif kronis, Anda berisiko lebih tinggi mengalami reaksi alergi. Reaksi alergi dapat muncul sebagai serangan asma (yang disebut asma analgesik), pembengkakan cepat (udem Quincke) atau ruam.
- Penting bagi Anda untuk diberi dosis terendah yang meredakan dan mengendalikan rasa sakit dan tidak diberikan obat ini lebih lama dari yang diperlukan untuk mengendalikan gejala Anda.
- Reaksi alergi dapat terjadi dengan obat ini, terutama pada awal pengobatan. Dalam hal ini, pengobatan harus dihentikan.
- Ada beberapa kasus meningitis aseptik dengan penggunaan obat ini. Risikonya lebih besar jika Anda menderita lupus eritematosus sistemik dan penyakit jaringan ikat terkait.
- Penggunaan secara bersamaan dengan AINS, termasuk inhibitor selektif siklooksigenase-2 harus dihindari.
- Reaksi GI yang serius dan berpotensi fatal: Gunakan dosis efektif terendah Ibuprofen jika diperlukan dosis yang singkat. Gunakan dengan hati-hati pada pasien dengan riwayat ulkus atau perdarahan GI.
- Kejadian trombotik CV yang serius dan berpotensi fatal: Gunakan dosis efektif terendah Bunafen untuk durasi sesingkat mungkin
- Efek pada hati: Efek ini bervariasi dari peningkatan transaminase kegagalan hati. Hentikan segera Bunafen jika tes fungsi hati yang abnormal menetap atau memburuk.
- Efek pada ginjal: Pemberian NSAID jangka panjang dapat menyebabkan nekrosis papiler ginjal, cedera ginjal lainnya, dan toksisitas ginjal pada pasien yang prostaglandin ginjalnya mempunyai peran kompensasi dalam pemeliharaan perfusi ginjal. Gunakan Bunafen dengan hati-hati pada pasien dengan risiko (misalnya lansia, pasien dengan gangguan fungsi ginjal, gagal jantung, gangguan fungsi hati, dan pasien yang mendapat diuretik atau *ACE inhibitor*).
- Reaksi anafilaktoid: Dapat terjadi pada pasien dengan triad asam salisilat. Hentikan segera pengobatan dengan Bunafen jika terjadi reaksi anafilaktoid.
- Efek hematologis: Dapat terjadi anemia. Pada pasien yang menerima terapi Ibuprofen jangka panjang, perlu dilakukan pemeriksaan hemoglobin atau hematokrit jika pasien menunjukkan tanda atau gejala anemia atau kehilangan darah**.** Hati-hati pada pada pasien dengan riwayat gangguan koagulasi atau pasien yang menerima antikoagulan.
- Hipertensi dapat terjadi dengan pengobatan NSAID. Monitor tekanan darah secara ketat selama pengobatan dengan Bunafen.
- Gagal jantung kongestif dan edema: retensi cairan dan edema dapat terjadi dengan pengobatan NSAID. Gunakan Bunafen dengan hati-hati pada pasien dengan retensi cairan atau gagal jantung.
- Menutupi peradangan dan demam : Aktivitas farmakologis Ibuprofen dalam mengurangi demam dan peradangan, sehingga dapat mengurangi tanda-tanda diagnostik dalam mendeteksi komplikasi dari kondisi yang dianggap tidak menular dan menyakitkan

<u>Infeksi</u>

Ibuprofen dapat menutupi tanda-tanda infeksi seperti demam dan nyeri. Oleh karena itu, dapat menyebabkan penundaan pengobatan infeksi yang tepat, dengan demikian dapat meningkatkan risiko komplikasi. Ini telah diamati pada pneumonia yang disebabkan oleh bakteri dan infeksi kulit

bakteri yang berhubungan dengan cacar air. Jika Anda minum obat ini saat Anda mengalami infeksi dan gejala infeksi Anda menetap atau memburuk, segera konsultasikan dengan dokter.
Secara umum, kebiasaan penggunaan (beberapa jenis) analgesik dapat menyebabkan masalah ginjal parah yang berlangsung lama.
Pada penggunaan obat penghilang rasa sakit yang berkepanjangan, sakit kepala dapat terjadi yang tidak boleh diobati dengan peningkatan dosis obat.

Ibuprofen dapat mengubah tes laboratorium berikut:
- Waktu perdarahan (dapat menjadi lebih panjang selama sehari setelah penghentian terapi)
- Konsentrasi glukosa darah (dapat menurun)
- Klirens kreatinin (dapat menurun)
- Hematokrit atau hemoglobin (dapat menurun)
- Urea nitrogen dalam darah, kreatinin plasma, dan kalium plasma (dapat meningkat)
- Tes fungsi hati: peningkatan nilai transaminase

Pemantauan
Karena ulserasi dan pendarahan saluran pencernaan yang serius dapat terjadi tanpa gejala, dokter harus memantau tanda-tanda atau gejala pendarahan saluran pencernaan. Pasien yang menjalani pengobatan jangka panjang dengan NSAID harus memeriksa profil kimia CBC (pemeriksaan darah lengkap) secara berkala. Jika timbul tanda dan gejala klinis yang sesuai dengan penyakit hati atau ginjal, timbul manifestasi sistemik (misalnya eosinofilia, ruam), atau kelainan tes hati menetap atau memburuk, hentikan Ibuprofen.

Penggunaan pediatrik
Keamanan dan efektivitas Ibuprofen untuk pengobatan nyeri tidak diketahui pada pasien anak di bawah usia 18 tahun.

Penggunaan geriatri
Studi klinis Ibuprofen tidak mencakup jumlah subjek yang berusia 65 tahun ke atas dalam jumlah yang cukup untuk menentukan apakah mereka memberikan respons yang berbeda dibandingkan subjek yang lebih muda. Pemilihan dosis untuk pasien lanjut usia harus dilakukan dengan hati-hati oleh dokter, biasanya dimulai dari kisaran dosis terendah, yang mencerminkan frekuensi penurunan fungsi hati, ginjal, atau jantung yang lebih besar, dan penyakit penyerta atau terapi obat lain. Pasien lanjut usia mempunyai peningkatan risiko terjadinya efek samping GI yang serius.

Obat-obatan lain dan Ibuprofen
Beri tahu dokter atau apoteker Anda jika Anda sedang mengonsumsi, baru saja mengonsumsi atau mungkin sedang mengonsumsi obat lain.
Ibuprofen dapat mempengaruhi atau dipengaruhi oleh beberapa obat lain. Sebagai contoh:
- Obat antiinflamasi nonsteroid (AINS) lainnya termasuk inhibitor COX-2 (misalnya celecoxib) dapat meningkatkan risiko tukak gastrointestinal dan perdarahan karena efek aditif.
- Obat-obatan yang bersifat antikoagulan (digunakan untuk mengencerkan/mencegah pembekuan darah seperti asam asetilsalisilat, warfarin, tiklopidin)
  Efek Warfarin dan NSAID pada perdarahan saluran cerna bersifat sinergis, sehingga pengguna kedua obat tersebut secara bersamaan memiliki risiko lebih tinggi mengalami perdarahan saluran cerna yang serius dibandingkan pengguna salah satu obat saja.
- Digoksin (digunakan untuk mengobati gagal jantung)
- Fenitoin (digunakan untuk mengobati epilepsi) atau litium (digunakan untuk mengobati depresi), dapat meningkatkan kadar obat-obatan tersebut dalam darah saat menggunakan Ibuprofen.
- Metotreksat (digunakan untuk mengobati jenis kanker atau rematik tertentu) yang diminum bersamaan dengan Ibuprofen (dalam kisaran 24 jam) dapat meningkatkan kadar dalam darah dan risiko toksisitas oleh metotreksat.
- Mifepristone yang di minum bersamaan antara 8-12 hari dapat menurunkan efek mifepristone.

- Antidepresan *selective serotonin reuptake inhibitor* (SSRI), seperti fluoxetine, juga dapat meningkatkan risiko perdarahan lambung dan usus.
- Obat-obatan yang menurunkan tekanan darah tinggi (inhibitor ACE seperti kaptopril, *beta-blocker* seperti atenolol, antagonis reseptor angiotensin-II seperti losartan)
- Kortikosteroid (seperti hidrokortison) (digunakan untuk peradangan) karena meningkatkan risiko tukak atau perdarahan pada lambung dan usus.
- Diuretik (seperti bendroflumethiazide), karena obat-obatan AINS dapat mengurangi efek obat ini dan dapat meningkatkan risiko pada ginjal.
- Obat-obatan yang mengandung probenesid dan sulfinpirazon dapat menunda pengeluaran zat sisa metabolisme Ibuprofen.
- Siklosporin dan tacrolimus (digunakan transplantasi) dapat meningkatkan risiko kerusakan ginjal.
- Sulfonilurea, seperti glibenklamid (obat yang digunakan untuk diabetes). Kontrol nilai glukosa darah dianjurkan ketika obat-obatan ini digunakan bersama-sama.
- Antibiotik golongan kuinolon, seperti ciprofloxacin karena peningkatan risiko kejang (*fits*).
- Vorikonazol, flukonazol (penghambat CYP2C9) (digunakan untuk infeksi jamur) dapat meningkatkan kadar Ibuprofen dalam darah.
- Zidovudine (digunakan untuk infeksi HIV) karena peningkatan risiko akumulasi darah pada sendi dan memar.
- Aminoglikosida (sejenis antibiotik). Obat AINS dapat menurunkan pengeluaran sisa metabolisme aminoglikosida.
- Antagonis H-2
- Ginkgo biloba (obat herbal yang sering digunakan pada demensia) dapat meningkatkan risiko perdarahan.

Beberapa obat lain juga dapat mempengaruhi atau dipengaruhi oleh pengobatan dengan Ibuprofen. Oleh karena itu, Anda harus selalu meminta saran dari dokter atau apoteker Anda sebelum Anda diberikan Ibuprofen dengan obat lain.

Ibuprofen dengan alkohol
Jika Anda minum alkohol pada waktu yang sama saat menerima obat ini, efek samping yang berhubungan dengan perut, usus dan sistem saraf dapat meningkat.

Kehamilan, menyusui dan kesuburan
Jika Anda sedang hamil atau menyusui, atau berpikir Anda mungkin hamil, atau sedang merencanakan untuk memiliki keturunan, mintalah saran dari dokter atau apoteker Anda sebelum Anda diberikan obat ini.
Ibuprofen tidak boleh diberikan selama trimester ketiga (3 bulan terakhir) kehamilan karena risiko penutupan dini duktus arteriosus dan potensi memperpanjang proses persalinan.
Selama trimester pertama dan kedua kehamilan, Ibuprofen hanya boleh digunakan jika benar-benar diperlukan.
Hanya sejumlah kecil Ibuprofen dan metabolitnya yang masuk ke dalam ASI. Karena efek berbahaya pada bayi belum diketahui hingga saat ini, perlu dibuat keputusan untuk menghentikan kegiatan menyusui atau menghentikan pemberian obat, dengan mempertimbangkan pentingnya obat untuk ibu.
Anda harus memberi tahu dokter Anda jika Anda berencana untuk hamil atau jika Anda memiliki masalah untuk hamil.

Mengemudi dan mengoperasikan mesin
Tidak ada tindakan pencegahan khusus yang diperlukan dalam pengobatan singkat. Namun, apabila pengobatan berkepanjangan, terjadinya efek samping, seperti kelelahan dan pusing dapat mengganggu kemampuan mengemudi dan/atau mengoperasikan mesin.

Ibuprofen mengandung natrium
Obat ini mengandung 371 mg sodium (komponen utama garam dapur) setiap botolnya. Ini setara dengan 18,6% dari asupan natrium harian maksimum yang direkomendasikan untuk orang dewasa.

3. Cara menggunakan Bunafen

Obat akan diberikan kepada Anda oleh dokter atau perawat.
Dosis yang dianjurkan untuk orang dewasa adalah 400 mg hingga 800 mg secara intravena setiap 6 jam sesuai kebutuhan. Minimal waktu infus adalah 30 menit. Dosis tertinggi yang dianjurkan adalah 2400 mg setiap hari, tidak boleh melebihi 3200 mg. Infus lebih dari 24 jam harus berdasarkan penilaian manfaat dibanding risiko.
Injeksi harus digunakan pada satu pasien pada satukali penggunaan. Bunafen tidak mengandung pengawet antimikroba. Larutan yang tidak digunakan harus dibuang.
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Jika Anda diberi lebih banyak Ibuprofen dari yang seharusnya
Jika Anda merasa telah diberi lebih banyak Ibuprofen dari yang seharusnya, segera berkonsultasi dengan dokter, apoteker, atau perawat Anda.

Gejalanya dapat berupa mual, sakit perut, muntah (mungkin berdarah), sakit kepala, telinga berdenging, kebingungan, dan gerakan mata bergetar (nistagmus). Pada dosis tinggi, kantuk, nyeri dada, jantung berdebar, kehilangan kesadaran, kejang (terutama pada anak-anak), ataksia, lemas dan pusing, darah dalam urin, kadar kalium yang rendah dalam darah, perasaan tubuh dingin, dan masalah pernapasan telah dilaporkan.

Anda mungkin juga menderita tekanan darah rendah, warna kebiruan pada kulit atau selaput lendir (sianosis), pendarahan ke perut atau usus, serta masalah fungsional hati dan ginjal.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mendapatkannya.
Efek samping dapat diminimalkan dengan menggunakan dosis efektif terendah untuk waktu sesingkat mungkin untuk mengobati gejala. Anda bisa mendapatkan satu atau lebih efek samping AINS yang diketahui (lihat di bawah). Jika Anda mengalami salah satu dari efek samping ini, Anda harus berhenti minum obat ini dan berkonsultasi dengan dokter sesegera mungkin. Pasien lanjut usia yang menggunakan obat ini memiliki risiko lebih besar untuk mengembangkan masalah yang terkait dengan efek samping.

Efek samping yang paling sering diamati adalah efek samping gastrointestinal (memengaruhi lambung dan usus). Tukak lambung (ulkus lambung atau usus), perforasi (lubang dinding lambung atau usus) atau perdarahan dari lambung atau usus, terkadang fatal, terutama dapat terjadi pada orang tua. Mual, muntah, diare, perut kembung, konstipasi, gangguan pencernaan, sakit perut, tinja yang tertinggal, muntah darah, stomatitis ulseratif (radang mukosa oral dengan ulserasi), eksaserbasi kolitis (radang usus besar) dan penyakit Crohn., Gastritis (radang lambung) lebih jarang terjadi.
Risiko terjadinya perdarahan ke dalam lambung dan usus tergantung pada dosis dan lama penggunaan.

- Kejadian trombotik kardiovaskular (lihat kotak ‘peringatan’)
- Efek pada saluran cerna (lihat kotak ‘peringatan’)
- Efek pada hati (lihat ‘Peringatan dan perhatian’)
- Hipertensi (lihat ‘Peringatan dan perhatian’)
- Jantung kongestif (lihat ‘Peringatan dan perhatian’)

• Efek pada ginjal (lihat ‘Peringatan dan perhatian’)
• Reaksi anafilaktoid (lihat ‘Peringatan dan perhatian’)
• Reaksi kulit yang serius (lihat ‘Peringatan dan perhatian’)

Berhenti menggunakan obat ini dan segera cari bantuan medis jika Anda mengalami:
- Tanda-tanda perdarahan usus, yang mungkin terjadi secara umum (dapat memengaruhi hingga 1 dari 10 orang), seperti sakit perut yang relatif parah, muntah darah atau partikel gelap yang terlihat seperti bubuk kopi, terkadang fatal, terutama pada orang tua.
- Tanda-tanda reaksi alergi yang sangat jarang tetapi serius (dapat memengaruhi hingga 1 dari 10.000 orang) seperti asma yang memburuk, mengi, atau sesak napas yang tidak dapat dijelaskan, pembengkakan pada wajah, lidah, atau tenggorokan, kesulitan bernapas, detak jantung yang cepat, penurunan darah tekanan yang menyebabkan syok yang mengancam jiwa. Ini dapat terjadi bahkan pada penggunaan pertama obat ini.
- Reaksi kulit yang sangat jarang yang parah (dapat mempengaruhi hingga 1 dari 10.000 orang) seperti ruam yang menutupi seluruh tubuh, kulit mengelupas, melepuh atau mengelupas (misalnya sindrom Stevens-Johnson, nekrolisis epidermal toksik/sindrom Lyell).
- Eksaserbasi peradangan yang berhubungan dengan infeksi (misalnya perkembangan necrotising fasciitis) yang terjadi bersamaan dengan penggunaan AINS telah dijelaskan sangat jarang (dapat mempengaruhi hingga 1 dari 10.000 orang).

<u>Sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang):</u>
- Kelelahan atau sulit tidur, sakit kepala dan pusing.
- Mulas, sakit perut, mual, muntah, perut kembung, diare, sembelit dan kehilangan sedikit darah di perut dan usus yang dapat menyebabkan anemia dalam kasus luar biasa.

<u>Umum (dapat mempengaruhi hingga 1 dari 10 orang):</u>
- Vertigo.
- Erupsi kulit.
- Nyeri dan sensasi terbakar di tempat pemberian.
- Ulkus gastrointestinal, berpotensi dengan perdarahan dan perforasi. Stomatitis ulseratif, eksaserbasi kolitis dan penyakit Crohn.

<u>Tidak umum (dapat mempengaruhi hingga 1 dari 100 orang):</u>
- Insomnia (masalah tidur), agitasi, lekas marah atau lelah, cemas dan gelisah.
- Gangguan penglihatan.
- Tinnitus (telinga berdenging atau berdengung).
- Penurunan produksi urin dan pembentukan edema, terutama pada pasien dengan tekanan darah tinggi atau masalah ginjal, sindrom nefrotik, nefritis interstisial yang mungkin disertai dengan insufisiensi ginjal akut.
- Urtikaria, pruritus, purpura (termasuk purpura alergi), ruam kulit.
- Reaksi alergi dengan ruam kulit dan gatal-gatal, serta serangan asma (mungkin dengan penurunan tekanan darah).
- Gastritis (radang lambung).

<u>Jarang (dapat mempengaruhi hingga 1 dari 1.000 orang):</u>
- Ambliopia toksik yang reversibel (penglihatan ganda).
- Kesulitan mendengar.
- Penyempitan esofagus (pembuluh darah di kerongkongan), komplikasi divertikula usus besar, kolitis hemoragik tidak spesifik. Jika terjadi pendarahan pada lambung atau usus, dapat menyebabkan anemia.
- Kerusakan jaringan ginjal (nekrosis papiler), terutama pada terapi jangka panjang, peningkatan konsentrasi asam urat serum dalam darah.

- Menguningnya kulit atau bagian putih mata, gangguan fungsi hati, kerusakan hati, terutama pada terapi jangka panjang, hepatitis akut (radang hati).
- Reaksi psikotik, gugup, lekas marah, bingung atau disorientasi dan depresi.
- Kaku pada leher.

Sangat jarang (dapat mempengaruhi hingga 1 dari 10.000 orang):
- Gangguan pembentukan sel darah (anemia, leukopenia, trombositopenia, pansitopenia, agranulositosis). Gejala pertama adalah: demam, sakit tenggorokan, sariawan di permukaan mulut, gejala seperti flu, kelelahan parah, pendarahan hidung dan kulit.
- Palpitasi (detak jantung cepat), gagal jantung, infark miokard.
- Hipertensi arteri
- Meningitis aseptik (leher kaku, sakit kepala, mual, muntah, demam atau bingung). Pasien dengan gangguan autoimun (SLE, penyakit jaringan ikat campuran) tampaknya memiliki kecenderungan.
- Radang kerongkongan atau pankreas, penyempitan usus.
- Asma, kesulitan bernapas (bronkospasme), sesak napas dan mengi.
- Lupus eritematosus sistemik (penyakit autoimun).
- Eritema, multiforme, rambut rontok (alopecia)
- Sensitivitas terhadap reaksi ringan dan radang pembuluh darah (vaskulitis)
- Dalam kasus luar biasa, infeksi parah pada kulit dan komplikasi jaringan lunak telah terjadi selama cacar air.

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia):
- Insufisiensi hati.
- Tempat reaksi injeksi seperti pembengkakan, memar atau pendarahan.
- Reaksi kulit parah yang dikenal sebagai sindrom DRESS dapat terjadi. Gejala DRESS meliputi: ruam kulit, demam, pembengkakan kelenjar getah bening dan peningkatan eosinofil (sejenis sel darah putih)
- Ruam merah bersisik luas dengan benjolan di bawah kulit dan lepuh terutama terlokalisasi pada lipatan kulit, badan, dan ekstremitas atas disertai demam pada permulaan pengobatan (pustulosis eksantema generalisata akut). Hentikan penggunaan Ibuprofen jika Anda mengalami gejala-gejala ini dan segera dapatkan bantuan medis. Lihat juga bagian 2.
- Selulitis, infeksi jamur saluran kemih, infeksi mikotik vulvovaginal
- Hipoestesia, sinkop, tremor
- Trombosis vena dalam, hematoma, pendarahan luka
- Batuk, sesak napas, mimisan, hidung tersumbat, edema faring, nyeri faringolaring, emboli paru, edema paru, depresi pernapasan, gagal napas, sindrom apnea tidur, *wheezing*
- Ketidaknyamanan perut, nyeri perut bagian atas, mulut kering, ileus, pencernaan yang terganggu (dispepsia)
- Luka drainase
- Selulitis, ulkus dekubitus, dermatitis alergi, hiperhidrosis, ruam
- Artralgia, nyeri punggung, nyeri leher, nyeri ekstremitas
- Hematuria, gagal ginjal akut, retensi urin
- Asidosis, hiperglikemia, hipoglikemia, hipomagnesemia, hiponatremia, hipokalemia
- Albumin darah menurun, kreatinin darah meningkat, glukosa darah meningkat, tekanan darah meningkat, pemeriksaan darah tidak normal, suara nafas tidak normal, enzim hati meningkat, tes fungsi hati tidak normal, saturasi oksigen menurun, jumlah trombosit menurun, keluaran urin menurun, hemoglobin menurun
- Anemia pasca operasi, infeksi luka pasca operasi, nyeri prosedur, komplikasi luka
- Nyeri dada, edema perifer, inflamasi, memar pada tempat infus, ekstravasasi tempat infus, iritasi pada tempat infus, kegagalan multiorgan
- Insufisiensi adrenal

- Nyeri dada, yang dapat menjadi gejala reaksi alergi yang berpotensi serius yang disebut Kounis Syndrome

Pelaporan efek samping
Apabila ada keluhan efek samping atau kondisi tidak nyaman selama dan setelah penggunaan obat, konsultasikan ke Dokter, Apoteker atau Perawat.
Anda dapat juga melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung melalui kontak berikut : pv.indonesia@fresenius-kabi.com. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat.

5. Cara menyimpan Ibuprofen

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada label dan karton setelah EXP. Tanggal kedaluwarsa mengacu pada hari terakhir bulan tersebut.
- Simpan dibawah suhu 30°C.
- Jangan dibekukan. Simpan botol di dalam karton luar agar terlindung dari cahaya.
- Obat ini harus digunakan segera setelah dibuka.
- Jangan gunakan obat ini jika Anda melihat ada partikel atau perubahan warna.
- Untuk sekali pakai saja. Setiap larutan yang tidak digunakan harus dibuang.
- Jangan membuang obat-obatan melalui air limbah. Tanyakan apoteker Anda bagaimana membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Kandungan Ibuprofen

- Zat aktifnya adalah Ibuprofen. Setiap mL larutan mengandung 4 mg ibuprofen. Setiap botol berukuran 100 mL mengandung 400 mg Ibuprofen.
- Zat tambahan:
    - Dinatrium Fosfat Dodekahidrat
    - Asam Hidroklorida (untuk penyesuaian pH)
    - Natrium Klorida
    - Natrium Dihidrogen Fosfat Dihidrat
    - Natrium Hidroksida (untuk penyesuaian pH)
    - Air untuk Injeksi

Bagaimana bentuk Ibuprofen dan isi kemasan
Ibuprofen 400 mg adalah larutan untuk infus yang bening dan tidak berwarna.
Larutan untuk infus dikemas dalam botol LDPE 100 mL setiap karton berisi 1 botol.

Diproduksi oleh:
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Bandung Barat, Indonesia

Reg No: DKI xxxxxxxxxxxxx
HARUS DENGAN RESEP DOKTER