

Package leaflet: Information for the user
Norfen 400 mg film-coated tablets
Ibuprofen

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

Always take this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse have told you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Norfen is and what it is used for
2. What you need to know before you take Norfen
3. How to take Norfen
4. Possible side effects
5. How to store Norfen
6. Contents of the pack and other information

1. What Norfen is and what it is used for

Ibuprofen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).

This medicine is indicated for the treatment of fever, the treatment of mild or moderate pain including migraine, the treatment of arthritis (inflammation of joints, usually affecting hands and feet, resulting in pain and swelling), juvenile rheumatoid arthritis, osteoarthritis (chronic disease resulting from joint cartilage damage), ankylosing spondylitis (inflammatory disease of the joints in the vertebral column), non-rheumatoid inflammation and primary dysmenorrhea (painful menstruation).

2. What you need to know before you take Norfen

Do not take Norfen

- If you are allergic to ibuprofen, to any other non-steroidal anti-inflammatory drugs (NSAIDs), to aspirin or to any of the other ingredients of this medicine (listed in section 6). Reactions pointing out this allergy may include: itchy skin rash, swelling of the face, lips or tongue, runny nose, difficulty in breathing or asthma.
- If you suffer from severe hepatic or renal diseases.
- If you have had an ulcer or bleeding in the stomach or small intestine (duodenum) or if you have suffered from gastrointestinal perforation.
- If you are vomiting blood.
- If you have diarrhoea passing blood in your stools or black stools.
- If you suffer from blood clotting or bleeding disorders, or if you are taking anticoagulants (blood-thinning medicines). If you need to take anticoagulants at the same time, your doctor shall run some tests for blood clotting.
- If you suffer from severe dehydration (caused by vomiting, diarrhoea or poor fluid intake).
- If you suffer from severe heart failure.
- If you are in the last three months of pregnancy.

Warnings and precautions

What you need to know before you take Norfen

Signs of an allergic reaction to this medicine, including breathing problems, swelling of the face and neck region (angioedema), chest pain have been reported with ibuprofen. Stop immediately Norfen and contact immediately your doctor or medical emergencies if you notice any of these signs.

Talk to your doctor, pharmacist or nurse before you start taking this medicine.

- If you have oedemas (fluid retention).
- If you suffer or have suffered any heart disorder or you suffer from high blood pressure.
- If you suffer from asthma or any other breathing problem.
- If you are receiving treatment with ibuprofen, given that it can mask the fever, which is a significant sign of infection, hindering the correct diagnosis.
- If you suffer from liver or kidney disease, you are over 60 years old, or you need to take this medicine for a prolonged period (over 1-2 weeks), your doctor may run some tests to monitor you regularly. Your doctor will advise about the regularity of monitoring controls.
- If you have had or if you develop stomach or duodenal ulcer, stomach or duodenal bleeding or perforation, leading to intense or persistent abdominal pain and/or passing black stools, or even with no previous alarm symptoms.
- The higher the dose and the longer the treatment, the higher the risk, particularly in patients with peptic ulcer background or elderly patients. In these cases, your doctor will consider co-administration of a medication to protect the stomach.
- If you are being coadministered any medication affecting blood clotting, such as oral anticoagulants or antiplatelet drugs similar to acetylsalicylic acid. You should also tell your doctor about any other medicine you are taking, which may increase the risk of bleedings, such as corticosteroids and selective serotonin reuptake inhibitor antidepressants.
- If you suffer Crohn's disease (chronic autoimmune inflammatory bowel disease causing inflammation that leads to bloody diarrhoea) or ulcerative colitis, since ibuprofen-like medicines may worsen these conditions.
- If you are under treatment with diuretics (medicines to increase urine output), since your doctor should monitor your kidney function.
- If you suffer from systemic lupus erythematosus (chronic disease affecting the immune system and multiple body organs, nervous system, blood vessels, skin and joints), since aseptic meningitis may occur (inflammation of meninges, the lining layers of brain and spinal cord, not caused by bacteria).
- If you suffer from acute intermittent porphyria (metabolic disorder affecting your blood, causing symptoms such as reddish urine, blood in urine or liver disease), so that the convenience of the treatment with ibuprofen can be assessed.
- If you suffer headaches after a prolonged treatment, do not take higher doses of this medicine.
- Allergic reactions to this medicine may develop.
- You will be monitored more closely by your doctor if you receive ibuprofen after undergoing major surgery.
- Do not take this medicine if you have chickenpox.

If you have an infection, see heading "Infections" below.

It is important to take the minimum dose that controls/relieves the pain, and this medicine should not be taken longer than needed to control your symptoms.

Take special care with Norfen:

Serious skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) have been reported in association with ibuprofen treatment. Stop using Norfen and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

Precautions in elderly patients

Elderly patients have an increased frequency of adverse reactions to NSAIDs (non-steroidal anti-

inflammatory drugs), especially gastrointestinal bleeding and perforation which may be fatal.

Skin reactions

Severe skin reactions associated with ibuprofen treatment have been reported. Stop taking ibuprofen and seek medical attention immediately if you develop any skin rash, lesions of the mucous membranes, blisters or other signs of allergy since this can be the first signs of a very serious skin reaction (see section 4).

Cardiovascular warnings

Anti-inflammatory/analgesic drugs like ibuprofen may be associated with a small increased risk for heart attack or stroke, especially when they are used in high doses. Do not exceed the recommended dose or duration of treatment.

You should talk to your doctor or pharmacist about your treatment before taking ibuprofen:

- If you have heart problems including heart failure, angina (chest pain) or if you have suffered a heart attack, bypass surgery, peripheral arterial disease (leg or feet circulation problems due to a narrowing or blockage of the arteries), or any type of stroke (including a “mini” stroke or transient ischemic attack “TIA”).
- If you have high blood pressure, diabetes, high cholesterol levels, a family history of heart diseases or stroke or if you smoke. This type of medicine may also cause fluid retention, especially in patients with heart failure and/or high blood pressure (hypertension).

Respiratory disorders

Caution should be exercised when administering ibuprofen to patients who suffer or have a history of bronchial asthma, chronic rhinitis or allergic diseases, since ibuprofen has been reported to cause bronchospasm, urticaria or angioedema in such patients.

Warnings during pregnancy and for women of childbearing age

Administration of ibuprofen-like medicines has been connected to a higher risk of suffering from miscarriage/congenital abnormalities, so ibuprofen is not recommended during the first and second trimester of the pregnancy unless strictly needed. In such cases, dose and duration will be as low as possible. The risk is believed to increase with dose and duration of therapy.

During the third trimester, ibuprofen administration is contraindicated.

Females of child-bearing age should be warned that ibuprofen-like medicines have been associated with a decreased ability to conceive.

Infections

Ibuprofen may hide signs of infections such as fever and pain. It is, therefore, possible that ibuprofen may delay appropriate treatment of infection, which may lead to an increased risk of complications. This has been observed in pneumonia caused by bacteria and bacterial skin infections related to chicken pox. If you take this medicine while you have an infection and your symptoms of the infection persist or worsen, consult your doctor without delay.

Other medicines and Norfen

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Ibuprofen may affect or be affected by other medicines. For example:

- Other non-steroidal anti-inflammatory drugs such as aspirin, since the risk of ulcer and gastrointestinal bleeding may increase.
- Antiplatelet drugs (they prevent clots or thrombi from occurring in blood vessels) such as ticlopidine.

- Cholestyramine (a medicine used to treat high cholesterol levels).
- Selective serotonin reuptake inhibitor antidepressants (used for depression).
- Lithium (medicine used to treat depression). It is likely that your doctor will adjust the dose of this medicine.
- Methotrexate (used for cancer and inflammatory diseases). It is likely that your doctor will adjust the dose of this medicine.
- Mifepristone (used to interrupt pregnancy).
- Digoxin and other cardiac glycosides (used in the treatment of heart disorders).
- Hydantoins such as phenytoin (used for treating epilepsy).
- Sulfonamides such as sulfamethoxazole and cotrimoxazole (used in the treatment of some bacterial infections).
- Corticosteroids such as cortisone and prednisolone.
- Diuretics (medicines used to increase urine output), since the risk of kidney toxicity may increase.
- Pentoxifylline (used to treat intermittent claudication).
- Probenecid (used to treat patients with gout or coadministered with penicillin for infections).
- Antibiotics of quinolone class such as norfloxacin.
- Sulfinpyrazone (to treat gout).
- Sulfonylureas such as tolbutamide (to treat diabetes), since it may cause hypoglycaemia.
- Tacrolimus or cyclosporin (to prevent organ transplant rejection).
- Zidovudine (antiretroviral for AIDS).
- Medicines that reduce high blood pressure (ACE inhibitors such as captopril, beta-blockers like medicines with atenolol and angiotensin II receptor antagonists like losartan).
- Thrombolytics (medicines used to dissolve clots).
- Aminoglycoside antibiotics such as neomycin.
- Herb extracts: *Ginkgo biloba* tree.
- Inhibitors of CYP2C9 (the responsible for the metabolism of a number of drugs in the liver), such as voriconazole and fluconazole (used to treat fungal infections).

Other medicines may also affect or be affected by treatment with ibuprofen. Therefore, you must always talk to your doctor or pharmacist before using ibuprofen with other medicines.

Interference with analytical tests

- Taking ibuprofen may alter the following laboratory tests:
- Bleeding time (it may last for 1 day after treatment discontinuation).
- Blood glucose level (it may decrease).
- Creatinine clearance (it may decrease).
- Haematocrit or haemoglobin (it may decrease).
- Blood urea nitrogen level, and serum creatinine and potassium level (it may increase).
- In liver function tests: increased transaminase values.

Talk to your doctor before undergoing any medical test and if you are taking or have recently taken ibuprofen.

Norfen with food, drink and alcohol

It may be taken alone or with food. It is generally recommended to take it with meals or with milk, thus reducing the chance of stomach upset. Do not take alcohol, as gastrointestinal adverse reactions may increase.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Ibuprofen should not be taken during pregnancy, especially during the third trimester.

Pregnancy

The use of this medicine is not recommended in women who are planning to become pregnant.

Do not take ibuprofen if you are in the last 3 months of pregnancy (see section “Warnings during pregnancy and for women of childbearing age”), as it could harm your unborn child or cause problems at delivery. It can cause kidney and heart problems in your unborn baby. It may affect your and your baby’s tendency to bleed and cause labour to be later or longer than expected. You should not take ibuprofen during the first 6 months of pregnancy, unless clearly necessary and as your doctor has told you. If you need treatment during this period or while you try to become pregnant, you should take the lowest dose for the shortest time possible. From pregnancy week 20, ibuprofen can cause kidney problems in your unborn baby, if taken longer than a few days, that may lead to low levels of amniotic fluid that surrounds the baby (oligohydramnios). If you need treatment for longer than a few days, your doctor may recommend additional monitoring.

Breast-feeding

Even though only small amounts of the medicine go to breast milk, taking ibuprofen for prolonged periods of time is not recommended during breast-feeding.

Therefore, tell your doctor if you get pregnant or you are breast-feeding.

Fertility

Females of child-bearing age should be warned that ibuprofen-like medicines have been associated with a decreased ability to conceive.

Driving and using machines

If you feel any dizziness, vertigo, changes in your vision or other symptoms while you are taking this medicine, you should not drive or use dangerous machinery.

If only a single dose of ibuprofen has been taken, or if ibuprofen is being taken during a short period of time, no extraordinary precautions are needed.

Ibuprofen may delay your reaction time, which should be considered before carrying out activities requiring increased attention, such as driving or operating machines.

This applies especially to the combination with alcohol.

This medicine contains less than 1 mmol sodium (23 mg) per ibuprofen tablet, that is to say essentially ‘sodium-free’.

3. How to take Norfen

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will tell you the duration of your treatment with ibuprofen. Do not discontinue treatment before told to do, since expected results would not be reached. Likewise, do not take ibuprofen for longer than your doctor told you to do.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms. If you have an infection, consult a doctor without delay if symptoms (such as fever and pain) persist or worsen (see section 2).

This medicine is for oral administration.

Patients feeling stomach upset should take this medicine with milk and/or with meals.

The recommended dose is:

Adults and adolescents from 12 years of age (weight $\geq$ 40 kg):

The recommended dose for adults and adolescents from 12 years of age is one tablet (400 mg) every 6 to 8 hours, depending on the severity of the clinical condition and the response to the treatment. In some conditions higher doses may be needed, but a daily dose higher than 2,400 mg for adults or 1,600 mg for adolescents, 12 to 18 years old, is not recommended.

Use in children

This medicine is not recommended for children and adolescents under 40 kg or younger than 12 years old, since the ibuprofen dose this product contains is not suitable for the recommended dose in this age group.

Elderly patients

If you are aged over 60 years, your doctor may prescribe a lower dose than usual. If so, you could only increase the dose once your doctor has checked a good tolerance to this medicine from you.

Patients with kidney and/or liver disease

If you suffer from a kidney and/or liver disease, your doctor may prescribe you a lower dose than usual. If so, take just the exact dose prescribed by your doctor.

Method of administration

This medicine is for oral administration.

In order to achieve a faster onset of action, the dose may be taken on an empty stomach. It is recommended that patients with a sensitive stomach take ibuprofen with food.

Take ibuprofen with a sufficient amount of water. The tablets should be swallowed whole and not chewed, broken, crushed or sucked to avoid mouth discomfort and throat irritation.

If you feel that the effect of this medicine is too strong or too weak, talk to your doctor or pharmacist.

If you take more Norfen than you should

If you have taken more Norfen than you should or if a child have accidentally taken the medicine, consult a doctor or pharmacist immediately, specifying the medicine and quantity ingested, or go to the nearest hospital to get an opinion of the risk and advice on action to be taken. Taking this package and leaflet with you is recommended when attending consultation with your healthcare provider.

Overdose symptoms generally occur after 4 to 6 hours after the intake of ibuprofen.

Symptoms in case of overdose may include stomach pain, nausea, vomiting (which may contain bloody sputum), indifferent mood, headache, involuntary eye movements, ear buzzing, confusion and lack of muscle coordination.

Symptoms of drowsiness, chest pain, palpitations, loss of consciousness, convulsions (mainly in children), weakness and dizziness, blood in the urine, chills and breathing problems have been reported at high doses.

Cases of increased blood plasma acidity (metabolic acidosis), decreased body temperature, impaired kidney function, bleeding from the stomach and intestine, coma, transient loss of breath (apnoea), depression of the central nervous system and respiratory system have been rarely reported. Cases of cardiovascular toxicity (decreased blood pressure, decreased heart rate and increased heart rate) have also been reported.

If severe poisoning has occurred, renal failure and liver damage may occur. In these cases, your doctor shall take the appropriate measures.

In case of taking a significantly high amount, activated charcoal should be administered.

If you forget to take Norfen

Do not take a double dose to make up for a forgotten dose.

If you forget to take your dose, take it as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose and take the next dose at the usual time.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effect occurrence from medicines like ibuprofen is more common in patients older than 65 years.

Chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome.

Stop using ibuprofen and seek medical attention immediately if you notice any of the following symptoms:

- Reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms [exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis].
- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome).
- A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment (acute generalised exanthematous pustulosis).

Side effect occurrence is lower during short treatments and when using daily doses under the maximum recommended dose.

- **Common side effects** (may affect up to 1 in 10 people): Gastrointestinal bleeding, especially in elderly patients. Nausea, vomiting, diarrhoea, flatulence, dyspepsia (gastrointestinal secretion or motility disorder), constipation, heartburn, abdominal pain, blood in stools, vomiting blood, headache, dizziness or sensation of unsteadiness and fatigue have also been observed.
- **Uncommon side effects** (may affect up to 1 in 100 people): gastritis, duodenal ulcers, gastric ulcers, reddening of the skin, itching or tingling of the skin, hives, purpura (purple spots on the skin), skin reactions due to light, hypersensitivity, paraesthesia (feeling of numbness, tingling, clamping, etc. more common in hands, feet, arms or legs), drowsiness, insomnia, anxiety, hearing disorders, vision impairments, rhinitis (inflammation of the nasal mucosa), inflammation of the oral mucosa with ulcer formation (canker sores), gastrointestinal perforations, hepatitis (inflammation of the liver), abnormal liver function and jaundice (yellowing of the skin and eyes), asthma, bronchospasm, dyspnoea (shortness of breath) have been observed. Tubulointerstitial nephritis (kidney disorder), nephrotic syndrome (disorder characterized by protein in the urine and swelling of the body) and renal insufficiency (sudden loss of the kidneys' ability to function), acute renal failure and papillary necrosis (especially in prolonged use) associated with an increase in urea.
- **Rare side effects** (may affect up to 1 in 1,000 people):
Disorientation or confusion, depression, aggressiveness, nervousness, psychotic reaction, vertigo, tinnitus (bumps or sounds in the ear), hearing impairment, reversible toxic amblyopia, liver lesions, oedema (swelling caused by fluid accumulation in the tissues), optic neuritis, anaphylactic reaction (in case of a severe generalized hypersensitivity reaction, the signs may be swelling of the face, tongue and larynx, dyspnoea (shortness of breath), tachycardia, hypotension (anaphylaxis, angioedema or severe shock), aseptic meningitis (inflammation of the meninges, which are membranes that protect the brain and spinal cord, not caused by bacteria). In most of the reported aseptic meningitis cases with ibuprofen, patients had some kind of underlying autoimmune disease (such as systemic lupus erythematosus and other collagen diseases) posing a risk factor. Aseptic

meningitis symptoms that have been observed are stiff neck, headache, nausea, vomiting, fever or disorientation. Other side effects are lowered platelet and white blood cell levels (which may manifest as frequent infections with fever, chills or sore throat), lowered red blood cells (which may manifest as difficulty in breathing and pale skin), neutropenia (decreased neutrophils) and agranulocytosis (very large decrease in neutrophils), aplastic anaemia (bone marrow insufficiency to produce different cells), haemolytic anaemia (premature breakdown of red blood cells). First symptoms are: fever, sore throat, shallow mouth ulcers, flu-like symptoms, extreme exhaustion, bleeding and bruising of unknown causes.

- **Very rare side effects** (may affect up to 1 in 10,000 people): Pancreatitis, prolongation of bleeding time, lupus erythematosus (joint pain and fever), really serious bullous reactions including Stevens-Johnson syndrome (scattered lesions affecting the skin and two or more mucous membranes and purple lesions, usually in the trunk) and toxic epidermal necrolysis (mucous lesions and painful necrotic lesions and detachment of the epidermis), erythema multiforme (skin lesions), hair loss, erythema multiforme. Exceptionally, serious skin infections and soft tissue complications may arise during chickenpox. Liver failure (severe liver dysfunction), heart failure, myocardial infarction, hypertension.

Exaltation of inflammation-related infections has been observed while using NSAIDs. If there are signs of infection or these worsen during the use of ibuprofen, it is recommended to visit the doctor as soon as possible.

- **Frequency not known** (frequency cannot be estimated from the available data):
Exacerbation of colitis and Crohn's disease (a chronic autoimmune inflammatory bowel disease causing inflammation that usually leads to bloody diarrhoea).

A serious skin reaction known as DRESS may occur. Symptoms of DRESS include: skin rash, inflammation of lymph nodes and elevated eosinophils (a type of white blood cell). A red, scaly widespread rash with bumps under the skin and blisters mainly localized on the skin folds, trunk, and upper extremities, accompanied by fever at the initiation of treatment (acute generalized exanthematous pustulosis). See also section 2.

If you experience any of the following adverse effects, stop taking the treatment and go to your doctor immediately:

- Allergic reactions such as skin rash, swollen face, chest wheezing or difficulty in breathing.
- Vomiting blood or vomits that look like coffee grounds.
- Blood in the stools or diarrhoea with blood.
- Intense stomach ache.
- Bullae or significant desquamation of skin.
- Intense or persistent headache.
- Yellowish skin pigmentation (jaundice).
- Serious hypersensitivity (allergy) signs (see above in this section).
- Swollen limbs or liquid retention in arms or legs.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Norfen

Keep this medicine out of the sight and reach of children.

No special storage conditions are required.

Do not use this medicine after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. If you are not sure, ask your pharmacist how to throw away containers and medicines you no longer need. These measures will help protect the environment.

6. Contents of the pack and other information

What Norfen 400 mg film-coated tablets contains

- The active substance is ibuprofen. Each tablet contains 400 mg of ibuprofen.
- The other ingredients are:
Core: microcrystalline cellulose, tricalcium phosphate, sodium croscarmellose, povidone, stearic acid, talc.
Coating: hypromellose, titanium dioxide (E-171) and macrogol 6000, talc.

What Norfen looks like and contents of the pack

Norfen 400 mg comes in film-coated tablets. Tablets are biconvex, elongated, white or offwhite.

Each pack contains 30 tablets and hospital packs contain 500 tablets, in alveolar packaging (blister) of PVC-aluminium.

Not all pack sizes may be marketed in all countries.

Marketing Authorisation Holder and Manufacturer

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