Patient package insert according to Pharmacists' Regulations (Preparations) - 1986

This medicine can be sold with a physician's prescription only

IBUFEN® 600, CAPLETS

Each caplet contains Ibuprofen 600 mg.

Inactive ingredients and allergens in the medicine - see section 6 "Additional information" and in section 2 "Important information about some of the ingredients of the medicine".

Read this entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have any further questions, ask the doctor or pharmacist.

This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if you think that their illness is similar to yours.

This medicine is intended for adults and adolescents above the age of 12.

1. What is the medicine intended for?

Ibufen 600 is an anti-inflammatory and an analgesic medicine for arthritis and osteoarthritis; for the relief of mild to moderate pain, such as headache, toothache, menstrual pain, backache, muscle ache.

Therapeutic group: Ibuprofen belongs to non-steroidal anti-inflammatory drugs (NSAIDs) group.

2. Before using the medicine

Do not use the medicine if:

- You are hypersensitive (allergic) to the active ingredient (ibuprofen) or to any of the other ingredients this medicine contains (see section 6).
- You have suffered in the past from a hypersensitivity reaction (such as bronchospasm, asthma attacks, swellings of the nasal mucous membrane, skin reactions or sudden swelling) after taking aspirin or other NSAIDs.
- You suffer from unexplained blood disorders.
- You suffer or have suffered in the past from a gastrointestinal (GI) ulcer or bleeding (at least 2 distinct episodes of ulceration or bleeding).
- You have suffered in the past from GI bleeding or perforation related to previous NSAID therapy.
- You suffer from brain haemorrhage or other active bleeding.
- You suffer from severe liver or kidney impairment.
- You suffer from severe congestive heart failure.
- You suffer from severe dehydration (caused by e.g. vomiting, diarrhoea or insufficient consumption of liquid).
- You are in the last three months of pregnancy.

Special warnings regarding the use of the medicine
Consult the doctor or pharmacist before taking **Ibufen 600**.
If you have an infection - see section "Infections" below.

Signs of an allergic reaction, including breathing problems, swelling of the face and neck (angioedema), chest pain, have been reported as associated to this medicine. Stop using the medicine and seek medical attention immediately if you notice any of these signs.

Take special care while taking this medicine
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 the medicine and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

Side effects may be minimized by using the lowest dose for the shortest possible duration required to control symptoms.

- Safety in the gastrointestinal tract
  Try to avoid concomitant use of **Ibufen 600** with other NSAIDs, including COX-2 selective inhibitors.
- Elderly patients
  In elderly patients, side effects after taking NSAIDs are more frequent; especially bleeding and perforation in the stomach and intestines, which may possibly become life-threatening. An especially careful medical supervision is thus necessary in these patients.
- Bleeding, ulcers and perforation in the gastrointestinal (GI) tract
  GI bleeding, ulceration or perforation, even with fatal outcome, have been reported with all NSAIDs. They have occurred at any time during treatment, with or without warning symptoms or a previous history of serious GI events.
  The risk of GI bleeding, ulcer or perforation increases with increasing NSAID doses, in patients with a history of ulceration, especially with complications of bleeding or perforation (see in section 2 “Do not use the medicine if”) and in elderly patients. These patients should start treatment with the lowest possible dose.
  The doctor will consider combination therapy with agents protecting the stomach lining (e.g. misoprostol or proton pump inhibitors [PPI]) for these patients, and also for patients requiring concomitant low dose aspirin (acetylsalicylic acid), or other medicines likely to increase the risk of GI effects.
  If you have a history of side effects in the GI tract, particularly if you are elderly, you should report any unusual abdominal symptoms (especially GI bleeding) particularly in the beginning of treatment.
  You should be careful if you receive concomitant medicines that increase the risk of ulcers or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin re-uptake inhibitors (SSRIs), which are used to treat depression, for example, or anti-platelet agents such as aspirin (see below section "Drug interactions").
  You should stop taking Ibufen 600 if gastrointestinal (GI) bleeding or ulceration occurs.

NSAIDs should be given with caution to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as these conditions may worsen (see section 4 “Side effects”).

- Cardiovascular effects
  Anti-inflammatory medicines/painkillers like ibuprofen may be associated with a small increased risk of a heart attack or a stroke, especially if used in high doses. **Do not exceed the recommended dose or duration of treatment**.
  You should consult the doctor or pharmacist before taking Ibufen 600 if:
  - You suffer or have suffered in the past from heart disease, including heart failure and angina (chest pain), have had a heart attack, bypass surgery, peripheral artery disease (circulatory disorders in the legs or feet caused by constricted or blocked arteries), or any kind of stroke (including mini stroke or transient ischaemic attack “TIA”).
  - You suffer from high blood pressure, diabetes or high cholesterol levels or if there is a history of heart disorders or stroke in your family or if you are a smoker.
- Skin reactions
  Severe skin reactions have been reported in connection with ibuprofen treatment. Stop taking **Ibufen 600** and consult the doctor immediately at the appearance of a skin rash, lesions of the mucous membranes, blisters or other signs of an allergy, as these may be the first signs of a very severe skin reaction (see section 4).
  Avoid taking **Ibufen 600** during chickenpox (varicella infection).
- Infections
  Ibufen 600 may hide signs of infections such as fever and pain. It is therefore possible that **Ibufen 600** 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 chickenpox. If you take this medicine while you have an infection and your symptoms of the infection persist or worsen, consult a doctor without delay.
- **Ibufen 600 should only be used after the doctor carefully weighs the benefit-risk-ratio:**
  - If you suffer from certain congenital blood disorders (e.g. porphyria).
  - If you suffer from certain autoimmune disorders (systemic lupus erythematosus and mixed connective tissue disease).
- **Special medical supervision is necessary:**
  - In patients with impaired kidney or liver function.
  - In patients with dehydration.
  - Directly after large operations.
  - In patients who suffer from allergies (e.g. skin reactions to other medicines, asthma, hay fever), chronic swelling of the nasal mucous membrane or chronic respiratory diseases that narrow the airways.
- Acute hypersensitivity reactions (e.g. anaphylactic shock) have been reported very rarely. **Ibufen 600** must be discontinued at the first appearance of hypersensitivity reaction signs. Adequate therapeutic measures have to be taken by the medical staff.
- Ibuprofen may temporarily inhibit platelet function (platelet aggregation). Patients with coagulation disorders should therefore be monitored closely by the doctor.
- In long-term therapy with **Ibufen 600**, liver function, kidney function and blood count should be checked regularly.

- Inform the doctor or dentist about taking this medicine before operations.
- During prolonged use of painkillers, headaches may appear. They must not be treated by increasing the dose of the medicine. Consult the doctor if you suffer from frequent headaches despite taking **Ibufen 600**.
- Generally, habitual intake of painkillers, especially a combination of several analgesic active ingredients, may permanently harm the kidneys and increase the risk for renal failure (analgesic nephropathy).

- **Children and adolescents**
  There is a risk of renal impairments in dehydrated adolescents.
  Do not take **Ibufen 600** under the age of 12, since the active ingredient content is too high. For this age group, there are other ibuprofen preparations containing lower dosage of the active ingredient.

Drug interactions
If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist, since **Ibufen 600** may affect or be affected by other medicines.
Especially inform the doctor or pharmacist if you are taking:
- Anticoagulants (medicines to thin the blood/to prevent blood clotting, e.g. aspirin, warfarin, ticlopidine).
- Medicines to lower high blood pressure (e.g. ACE inhibitors like captopril, beta-blockers like atenolol, angiotensin II receptor antagonists like losartan).
- Digoxin (for the treatment of heart diseases), phenytoin (for the treatment of seizures) or lithium (for the treatment of mental disorders) - combination of **Ibufen 600** with any of these medicines may increase their concentration in the blood. Blood level of lithium must be monitored. It is recommended to monitor blood levels of digoxin and phenytoin.
- Diuretics or medicines to lower blood pressure. **Ibufen 600** may reduce the effect of these medicines.
- ACE inhibitors (for the treatment of heart failure and high blood pressure) - **Ibufen 600** may reduce the effect of these medicines. Concomitant administration may also increase the risk of sudden renal failure.
- Potassium-sparing diuretics - concomitant administration with **Ibufen 600** may cause an increased potassium level in the blood.
- Anti-inflammatory medicines and other analgesics of the NSAID group or glucocorticoids - concomitant administration of **Ibufen 600** increases the risk of GI ulcer or bleeding.
- Anti-platelet agents and certain antidepressants (SSRIs) may increase the risk of GI bleeding.
- Methotrexate - taking **Ibufen 600** within 24 hours before or after administration of methotrexate (mainly for the treatment of neoplastic diseases, psoriasis and rheumatoid arthritis) may cause an increased methotrexate concentration and to an increase of its side effects.
- Ciclosporin (medicine to prevent transplant rejection or for the treatment of rheumatism) - concomitant administration with certain NSAIDs increases the risk for the kidney-damaging effect of ciclosporin. This effect cannot be ruled out for a combination of ciclosporin with ibuprofen.

- Medicinal products containing probenecid or sulfinpyrazone (for the treatment of gout) may delay ibuprofen excretion. This may lead to an accumulation of Ibuprofen in the body and to an increase of its side effects.
- Anticoagulants like warfarin - NSAIDs may increase the anticoagulant effect of these medicines. In concomitant use, it is recommended to monitor coagulation.
- Sulfonylurea (medicine to lower blood sugar levels) - clinical trials have shown interaction between NSAIDs and this medicine. When ibuprofen and sulfonylurea are used concomitantly, surveillance of blood glucose levels is recommended as a precaution.
- Tacrolimus - there is an increased risk of nephrotoxicity when ibuprofen is administered with tacrolimus.
- Zidovudine - there is evidence of an increased risk of bleeding in the joints and haematoma in HIV positive haemophiliacs receiving concomitant treatment with zidovudine and ibuprofen.
- Quinolone antibiotics (e.g. ciprofloxacin) - taking the two medicines at the same time increases the risk of seizures.
- CYP2C9 enzyme inhibitors (e.g., fluconazole, voriconazole) - concomitant use of ibuprofen and CYP2C9 inhibitors may increase exposure to ibuprofen (which is broken down by CYP2C9 enzyme). In a study involving voriconazole and fluconazole (CYP2C9 inhibitors), the exposure to ibuprofen was approximately 80-100% higher. Reducing the ibuprofen dosage should be considered when potent CYP2C9 inhibitors are used concomitantly, especially if high doses of ibuprofen are administered with either voriconazole or fluconazole.
- Ginkgo biloba (a herbal medicinal product) may increase the NSAID-related risk of bleeding.
- Mifepristone - NSAIDs should not be taken 8-12 days after taking mifepristone, since these medicines may reduce the effect of mifepristone.

Use of the medicine and alcohol consumption
Consuming alcohol may amplify side effects related to the active substance, especially those affecting the central nervous system or the gastrointestinal tract. Therefore, avoid drinking alcohol whilst taking **Ibufen 600**.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning to become pregnant, consult a doctor or a pharmacist before taking this medicine.
Pregnancy
Consult the doctor if you become pregnant while using **Ibufen 600**. You should consult the doctor before taking ibuprofen in the first and second trimester of pregnancy.
You should not take **Ibufen 600** during the first 6 months of pregnancy, unless absolutely necessary and recommended by your doctor. If you need treatment during this period or while you are trying to get pregnant, the lowest dose for the shortest time possible should be used.
This medicine has possible side effects of foetal kidney impairment and low levels of amniotic fluid or narrowing of a blood vessel in the heart of the unborn baby at about 20 weeks or later in pregnancy. It is recommended to avoid using NSAIDs at about 20 weeks or later in pregnancy and to consult a healthcare professional if necessary.

In the last trimester of pregnancy, you must not take **Ibufen 600** due to an increased risk of complications for the mother and child.
The medicine can cause kidney and heart problems in the unborn baby and may affect your and your baby's tendency to bleed and cause labour to be later or longer than expected.
Breastfeeding
The active ingredient ibuprofen and its decomposition products pass into breast milk in low concentrations only. As adverse effects for the baby are not known, stopping breastfeeding is usually not necessary during short-time treatment with ibuprofen. However, if a longer duration of treatment or higher doses are prescribed, early stopping of breastfeeding should be considered.
Fertility
Ibufen 600 may make it more difficult to become pregnant. Inform the doctor, if you plan to become pregnant or if you have problems becoming pregnant.

Driving and using machines
High doses of **Ibufen 600** may cause adverse reactions affecting the central nervous system such as fatigue and dizziness. In individual cases, this may influence the response time and impair the ability to drive and to operate machines. This is all the more true in combination with alcohol. You will not be able to respond to unexpected and sudden events with a sufficiently quick and focused reaction. In this case, do not drive a car! Do not operate tools or machines! Do not work without a safe grasp!
As for children, they should be warned to be careful when riding a bicycle or playing near roads etc.

Important information about some of the ingredients of this medicine
This medicine contains less than 1 mmol sodium (23 mg) per caplet, that is to say essentially "sodium-free".

3. How to use this medicine?

Always use this medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about the dosage and the manner of treatment with the medicine.
The dosage and administration will be determined by the doctor only. The usual recommended dosage is:
One caplet, twice a day.
The dosage for children above the age of 12 should be determined according to their body weight.
Do not exceed the recommended dose.

Duration of treatment
In rheumatic disorders, the treatment with **Ibufen 600** may be necessary for a long period of time. The duration of treatment will be determined by the treating physician. Take the lowest effective dose for the shortest duration necessary to relieve the symptoms. If you have an infection, consult the doctor urgently if the symptoms (such as fever and pain) continue or worsen (see section 2).

Method of administration

Swallow the caplet with water and not on an empty stomach. If you have a sensitive stomach, you should take **Ibufen 600** with food.
The caplet may be halved. Do not crush or chew the caplet to avoid the bitter taste of the medicine.
Take **Ibufen 600** according to the doctor's instructions. If you do not feel an adequate relief of pain, do not take a higher dosage without consulting the doctor. Consult the doctor if you think the effect of **Ibufen 600** is too strong or too weak.

If you have accidentally taken a higher dosage
If you took an overdose or if a child has accidently swallowed the medicine, refer immediately to a doctor or to a hospital emergency room to get an opinion of the risk and advice on action to be taken. Bring the medicine package with you.

The symptoms of overdose can include nausea, stomachache, vomiting (may be blood-streaked), headache, ringing in the ears, confusion and shaky eye movement. Also, bleeding in the gastrointestinal tract may occur. At high doses, drowsiness, light-headedness, chest pain, palpitations, loss of consciousness, convulsions (mainly in children), weakness and dizziness, blood in urine, impairment of liver and kidney function, reduced breathing (respiratory depression), drop in blood pressure, blue-red coloration of skin and mucous membranes (cyanosis), cold body feeling, and breathing problems have been reported.

There is no specific antidote.

If you forgot to take the medicine
If you forgot to take the medicine at the set time, do not take a double dose. Take the dose as soon as you remember, unless it is almost time for the next dose. Never take a double dose to compensate for the missed dose.
Continue with the treatment as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take the medicine. Wear glasses if you need them.
If you have any further questions on the use of this medicine, consult the doctor or pharmacist.

4. <u>Side effects</u>

Like any medicine, the use of **Ibufen 600** may cause side effects in some users. Do not be alarmed while reading the list of side effects. You may not suffer from any of them.
The side effects are classified according the following frequencies:
Very common (effects that occur in more than 1 in 10 users).
Common (effects that occur in 1-10 out of 100 users).
Uncommon (effects that occur in 1-10 out of 1,000 users).
Rare (effects that occur in 1-10 out of 10,000 users).
Very rare (effects that occur in less than 1 in 10,000 users).
Unknown frequency (effects for which frequency has not yet been established).

Possible side effects:

The following side effects depend mainly on the dosage and may vary individually; this has to be taken into account.
The most common side effects are GI in nature. GI ulcer, perforation or bleeding, sometimes fatal, particularly in the elderly, may occur (see section 2 “Before using the medicine”). Nausea, vomiting, diarrhoea, flatulence, constipation, digestive problems, abdominal pain, black stool, blood vomiting, ulcerative stomatitis, worsening of colitis and Crohn's disease (see section 2) have been reported following use. Less frequently, incidences of gastritis have been reported. The risk of GI bleeding depends mainly on the dose and the duration of treatment.
Oedema, high blood pressure and heart failure have been reported in association with NSAIDs therapy.
Medicinal products like **Ibufen 600** may be associated with a slightly increased risk of a heart attack or a stroke.

Stop using the medicine and refer immediately to a doctor if the following side effects appear:

- **Cardiac side effects:**
  Unknown frequency: chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome.
- **Blood side effects:**
  Abnormal blood formation (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis) - very rare. Early signs may be: fever, sore throat, superficial lesions in the mouth, flue-like symptoms, severe exhaustion, nosebleed and skin bleeding.
  In these cases, do not take pain killers or fever-lowering medicines on your own.
  During a long-term treatment, blood count test should be performed regularly.
- **Immune system side effects:**
  Uncommon: hypersensitivity reactions with skin rash, itching of the skin and asthma attacks (possibly with drop in blood pressure).
  Very rare: severe general hypersensitivity reactions. They may manifest in swelling of the face, tongue and throat with constriction of the airways, breathing difficulties, fast heartbeat, wheezing, drop in blood pressure and even dangerous shock.
  At the appearance of any of these signs, which may appear at the first dose of the medicine, immediate medical care is necessary.
- **Gastrointestinal side effects:**
  Severe pain in the upper stomach, blood or coffee ground coloured vomit, bloody and/or black stool.
- **Skin and subcutaneous tissue side effects:**
  Very rare: severe skin reactions, such as skin rash with reddening, reddish non-elevated, target-like or circular patches on the trunk, peeling, blistering, ulcers in the mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (e.g. exfoliative dermatitis, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis).
  Unknown frequency: serious widespread rash, high body temperature, enlarged lymph nodes and an increase in the level of eosinophils (a type of white blood cells) - DRESS syndrome; at the beginning of treatment may occur a red, scaly widespread rash with bumps under the skin and blisters localized mainly on the skin folds, the torso and the upper extremities accompanied by fever - acute generalised exanthematous pustulosis (AGEP). (See section 2).
- **Kidney system side effects:**

Uncommon: increased water retention in the tissue with oedema formation, especially in patients with high blood pressure or with impaired kidney function, nephrotic syndrome (water accumulation in the body - oedema, and excess protein in the urine), inflammatory kidney disorder (interstitial nephritis), which may be associated with an acute kidney dysfunction.
Very rare: renal tissue lesions and increase in blood level of uric acid.
Reduced urination, accumulation of water in the body (oedema), and generally feeling unwell may be first signs of a kidney disorder or even kidney failure.

- **Eye side effects:**
  Uncommon: visual disorders.

Refer to a doctor immediately at the appearance or worsening of infection signs (e.g. reddening, swelling, overheating, pain, fever).

Additional side effects:

- **Infections and parasitic diseases:**
  Very rare: worsening of infection-related inflammations (e.g. development of necrotizing fasciitis) has been reported while treatment with certain NSAIDs (including **Ibufen 600**).
  Very rare: aseptic meningitis - the symptoms may include strong headache, nausea, vomiting, fever, stiff neck or disorientation, intolerance to bright light. Patients suffering from certain autoimmune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) seem to be at increased risk.
- **Psychiatric side effects:**
  Very rare: psychotic reactions, depression.
- **Nervous system side effects:**
  Common: disturbances of the central nervous system, such as headache, dizziness, difficulty sleeping, excitation, irritability or fatigue.
- **Hearing system side effects:**
  Very rare: ringing in the ears (tinnitus), hearing loss.
- **Cardiac side effects:**
  Very rare: palpitations, oedema (fluid retention), heart failure, heart attack.
- **Vascular side effects:**
  Very rare: high blood pressure (arterial hypertension).
- **Gastrointestinal (GI) side effects:**
  Very common: GI complaints like heartburn, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation and low GI bleeding, which may cause anaemia in exceptional cases.
  Common: GI ulcer (peptic ulcer), possibly with bleeding and perforation. Ulcerative stomatitis, worsening of colitis or of Crohn's disease.
  Uncommon: stomach inflammation (gastritis).
  Very rare: inflammation of the oesophagus, of the pancreas (pancreatitis), formation of membranous constrictions in the small and large intestine.
- **Liver and gall-bladder side effects:**
  Very rare: liver dysfunction, liver damage, especially in long-term therapy, liver failure, acute inflammation of the liver (hepatitis). In long-term treatment, hepatic parameters should be checked regularly.
- **Skin and subcutaneous tissue side effects:**

Very rare: hair loss.
Skin sensitivity to light.
There have been exceptional cases of severe skin infection and soft tissue complications during a chickenpox infection.

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult the doctor.

Side effects can be reported to the Ministry of Health by clicking the link "דיווח על תופעות לוואי עקב טיפול תרופתי" found on the homepage of the Ministry of Health website (www.health.gov.il) directing to the online form for reporting side effects or via the link: https://sideeffects.health.gov.il

5. How to store the medicine?

- Avoid poisoning! This medicine and any other medicine must be stored in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use this medicine after the expiry date (תאריך תפוגה) stated on the package. The expiry date refers to the last day of that month.
- **Storage conditions:** Store in a dry place. Do not store above 25°C.
- Do not throw away any medicines via wastewater or household waste. Ask the pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredient, this medicine also contains:
Microcrystalline cellulose, maize starch, croscarmellose sodium, magnesium stearate, hypromellose, carmellose sodium, silica colloidal anhydrous, titanium dioxide (E171), stearic acid, talc, macrogol 400, carnauba wax.

What the medicine looks like and what the package contains:
White caplets with a score line on both sides.
Approved package sizes: 15, 30 or 1000 caplets.
Not all pack sizes may be marketed.

Revised in March 2024 according to MOH guidelines.

Drug registration number at the national medicines registry of the Ministry of Health: 040-23-26009-00

Manufacturer and registration holder: Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel.