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 this 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 the same as 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 use of other NSAIDs.
- 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 fluid intake).
- 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.

Side effects may be minimized by using the lowest dose for the shortest duration necessary 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. Special medical supervision is 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 signs or a previous history of serious GI events.
  The risk of GI bleeding, ulcer or perforation increases with increasing NSAIDs dose, 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 medicine protecting the stomach lining (such as 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 at the beginning of treatment.
  You should exercise extra caution if you take additional 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 medicines 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 diseases (ulcerative colitis, Crohn's disease) as these conditions may worsen (see section 4 “Side effects”).
- Cardiovascular effects
  Anti-inflammatory medicines/painkillers such as 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 you have a family history of heart disease or stroke, or if you are a smoker.

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.

- Skin reactions
  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.

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 (such as 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.
  - Immediately after major surgeries.
  - In patients who suffer from allergies (such as 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 (such as anaphylactic shock) have been reported very rarely. **Ibufen 600** must be discontinued at the first appearance of hypersensitivity reaction signs. The medical staff will provide treatment as needed.
- Ibuprofen may temporarily inhibit platelet function (platelet aggregation). Patients with coagulation disorders should therefore be carefully monitored by the doctor.
- During 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 surgeries.
- During prolonged use of painkillers, headaches may occur. They should 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 damage the kidneys and increase the risk of kidney failure (analgesic nephropathy).

- **Children and adolescents**
  There is a risk of impaired kidney function in children and adolescents who are dehydrated. **Ibufen 600** should not be taken by children under the age of 12, since the active ingredient content is too high. For this age group, there are other ibuprofen medicines containing a lower amount 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 for blood thinning/ preventing blood clotting, such as aspirin, warfarin, ticlopidine).
- Medicines that reduce high blood pressure (such as 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 reduce blood pressure. **Ibufen 600** may weaken the effect of these medicines.
- ACE inhibitors (for the treatment of heart failure and high blood pressure) - **Ibufen 600** may weaken the effect of these medicines. Concomitant administration may also increase the risk of sudden kidney failure.
- Potassium-sparing diuretics - concomitant administration with **Ibufen 600** may increase potassium level in the blood.
- Anti-inflammatory medicines and other analgesics of the NSAIDs group or glucocorticoids - concomitant administration of **Ibufen 600** increases the risk of gastrointestinal ulcer or bleeding.
- Anti-platelet medicines and certain antidepressants (SSRIs) may increase the risk of gastrointestinal bleeding.
- Methotrexate - taking **Ibufen 600** within 24 hours before or after administration of methotrexate (mainly for the treatment of malignant diseases, psoriasis and rheumatoid arthritis) may cause an increased methotrexate concentration and increase in side effects.
- Ciclosporin (a medicine for preventing transplant rejection and treating rheumatism) - concomitant administration with certain NSAIDs increases the risk for kidney-damaging effect of ciclosporin. This effect cannot be ruled out for a combination of ciclosporin and ibuprofen.
- Medicinal products containing probenecid or sulfinpyrazone (for the treatment of gout) may delay ibuprofen excretion. This may lead to accumulation of Ibuprofen in the body and to an increase in side effects.
- Anticoagulants such as warfarin - NSAIDs may increase the anticoagulant effect of these medicines. When used concomitantly, it is recommended to monitor coagulation function.
- Sulfonylurea (a medicine for lowering blood sugar levels) - clinical trials have shown interaction between NSAIDs and this medicine. When using ibuprofen and sulfonylurea concomitantly, it is recommended to monitor blood sugar levels 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 joint bleeding and haematoma in HIV positive haemophiliacs receiving concomitant treatment with zidovudine and ibuprofen.
- Quinolone antibiotics (such as ciprofloxacin) - taking both medicines at the same time increases the risk of seizures.
- CYP2C9 enzyme inhibitors (such as fluconazole, voriconazole) - concomitant use of ibuprofen and CYP2C9 inhibitors may increase exposure to ibuprofen (which is broken down by the 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 concomitantly with voriconazole or fluconazole.
- Ginkgo biloba (a herbal medice) 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 ingredient, especially those affecting the central nervous system or 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 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.
Do 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 as of the 20th week of pregnancy. It is recommended to avoid using medicines of the NSAIDs class as of the 20th week of pregnancy and consult a healthcare professional, if necessary.
In the last trimester of pregnancy, **Ibufen 600** must not be taken due to an increased risk of complications for both the mother and the baby.
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 only in low concentrations. Since no side effects have been reported in infants, there is usually no need to stop breastfeeding during short-time treatment with ibuprofen. However, if a long-term treatment or higher doses are prescribed, early discontinuing of breastfeeding should be considered.
Fertility
Ibufen 600 may make it more difficult to become pregnant. Inform the doctor, if you are planning 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 operate machinery. This is especially true when combined 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 machinery! Do not work without a secure grip!
As for children, they should be warned about riding a bicycle or playing near roads etc.

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

3. How should you use the 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 manner of treatment will be determined by the doctor only. The usual recommended dosage is:
One caplet, twice a day.
The dosage regimen in 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 diseases, the treatment with **Ibufen 600** may be necessary for a longer period. The duration of treatment will be determined by the attending physician.
Take the lowest effective dose for the shortest duration necessary to relieve symptoms. If you have an infection, consult the doctor urgently if symptoms (such as fever and pain) persist 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 can 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 have taken an overdose or if a child has accidently swallowed the medicine, proceed immediately to a doctor or a hospital emergency room to get an opinion of the risk and advice on action to be taken. Bring the package of the medicine with you.
The symptoms of overdose can include nausea, stomach ache, vomiting (may be blood-streaked), diarrhoea, headache, ringing in the ears, confusion and shaky eye movement. Also, gastrointestinal bleeding may occur.In addition, symptoms of agitation, sleepiness, disorientation or coma may occur. Sometimes patients develop convulsions. At high doses, drowsiness, light-headedness, chest pain, palpitations, loss of consciousness, convulsions (mainly in children), weakness and dizziness, blood in urine, low levels of potassium in the blood, impairment of liver and kidney function, reduced breathing (respiratory depression), drop in blood pressure, blue color of the skin and mucous membranes (cyanosis), cold body feeling, and breathing problems have been reported. Moreover, the prothrombin time/INR might be prolonged, probably due to an impairment in the activity of coagulation factors in the blood system. Acute renal failure and liver damage might occur. Exacerbation of asthma in asthmatics may occur.
There is no specific antidote.

If you forgot to take the medicine
If you forgot to take this medicine at the designated 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 make up for a forgotten dose.

Continue with the treatment as recommended by the doctor.
Even if there is an improvement in your health, do not stop taking this medicine 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 when reading the list of side effects. You may not suffer from any of them.

The following side effects are primarily dose-dependent and may vary from patient to patient. This should be taken into consideration.
The most common side effects are gastrointestinal in nature. Gastrointestinal 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 gastrointestinal bleeding is primarily dependent on the dosage and duration of treatment.

Oedema, high blood pressure and heart failure have been reported in association with NSAIDs therapy.
Medicinal products such as **Ibufen 600** may be associated with a slightly increased risk of heart attack or stroke.

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

Common side effects (effects that occur in 1-10 out of 100 users):
- Severe upper abdominal pain, vomiting blood or coffee-ground-like material, blood in the stool and/or black stool.

Uncommon side effects (effects that occur in 1-10 out of 1,000 users):
- Hypersensitivity reactions with skin rash, itching of the skin and asthma attacks (possibly with drop in blood pressure).
- Visual disorders
- Increased water retention in the tissue with oedema formation, especially in patients with high blood pressure or impaired kidney function, nephrotic syndrome (water retention in the body - oedema, and excess protein in the urine), inflammatory interstitial kidney disorder (interstitial nephritis), which may be accompanied by acute kidney failure. Decreased urination, water retention in the body (oedema), and a general feeling of being unwell may be early symptoms of kidney disorder and even kidney failure.

Very rare side effects (effects that occur in less than 1 in 10,000 users):
- Worsening of infection-related inflammations (such as development of necrotizing fasciitis) has been reported during treatment with certain NSAIDs (including ibuprofen). Contact a doctor immediately at the appearance or worsening of infection signs (such as redness, swelling, overheating, pain, fever).
- Aseptic meningitis - the symptoms may include strong headache, nausea, vomiting, fever, stiff neck or disorientation. Patients suffering from certain autoimmune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) are at increased risk.
- Disorders of blood cell formation (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis). Early signs may include: fever, sore throat, superficial lesions in the mouth, flue-like symptoms, severe fatigue, nasal and skin bleeding. In these cases, do not take painkillers or fever-lowering medicines at your discretion. During a long-term treatment, blood count tests should be performed regularly.
- Severe generalized hypersensitivity reactions. These may manifest as swelling of the face, tongue and throat with constriction of the airways, breathing difficulties, fast heartbeat, drop in blood pressure and even dangerous shock.
  These may appear even after the first dose of the medicine.
- Serious skin reactions, such as skin rash with redness, reddish non-elevated, target-like or circular patches on the trunk, skin peeling, blisters, ulcers in the mouth, throat, nose, genitals and eyes. These early signs of serious skin rashes can be preceded by fever and flu-like symptoms (such as exfoliative dermatitis, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis).

Side effects with unknown frequency (effects for which a frequency has not yet been determined):
- Chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome.
- Serious widespread rash, high body temperature, enlarged lymph nodes and an increased level of eosinophils (a type of white blood cells) - drug reaction with eosinophilia and systemic symptoms (DRESS syndrome).

- A red, scaly widespread rash with bumps under the skin and blisters mainly localized on the skin folds, the trunk and the upper extremities accompanied by fever - acute generalised exanthematous pustulosis (AGEP) may appear at the beginning of treatment.

There have been exceptional cases of severe skin infection and soft tissue complications during a chickenpox infection.

Additional side effects:

Very common side effects (effects that occur in more than 1 out of 10 users):
- Gastrointestinal complaints such as heartburn, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation and bleeding in the lower Gastrointestinal tract, which may cause anaemia in exceptional cases.

Common side effects (effects that occur in 1-10 out of 100 users):
- Disturbances of the central nervous system, such as headache, dizziness, insomnia, agitation, irritability or fatigue.
- Gastrointestinal ulcer (peptic ulcer), possibly with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis or Crohn's disease.

Uncommon side effects (effects that occur in 1-10 out of 1,000 users):
- Inflammation of the stomach lining (gastritis).

Rare side effects (effects that occur in 1-10 out of 10,000 users).
- Ringing in the ears (tinnitus), hearing loss.

Very rare side effects (effects that occur in less than 1 in 10,000 users):
- Psychotic reactions, depression.
- Palpitations, oedema (fluid retention), heart failure, heart attack.
- High blood pressure (arterial hypertension).
- Inflammation of the oesophagus, Inflammation of the pancreas.
- Liver dysfunction, liver damage, especially in long-term use, liver failure, acute inflammation of the liver (hepatitis). During long-term treatment, liver function tests should be monitored regularly.
- Hair loss.
- Kidney tissue lesions and an increase in blood uric acid levels.
- Formation of membranous constriction in the small and large intestine

Side effects with unknown frequency (effects for which a frequency has not yet been determined):
- Sensitivity of the skin to light.

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 October 2024 according to MOH guidelines.

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

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