SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibufen 600

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each caplet contains 600 mg ibuprofen.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Caplet

White, biconvex, film-coated caplets, scored on both sides.

The caplet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of mild to moderate pain such as headache, toothache, primary dysmenorrhea, backache, muscular pain.
Anti-inflammatory and analgesic in arthritis and osteoarthritis.

4.2 Posology and method of administration

Posology

Rheumatic disorders:
The ibuprofen dose depends on age and/or body weight.
The recommended daily dose for adults is 1,200 mg in divided doses. In severe or acute conditions, it can be advantageous to increase the dosage to 1600 mg daily; in divided doses. The maximum single dose for adults should not exceed 800 mg ibuprofen.
The duration of treatment is determined by the attending physician.
In rheumatic disorders, the use of **Ibufen 600** may be necessary over a longer period of time.

Undesirable effects may be minimized by using the lowest effective dose for the shortest possible duration to control symptoms (see section 4.4).

Special populations

Elderly patients

No special dose adjustment is necessary. Due to the possible adverse event profile (see section 4.4), elderly patients should be carefully monitored.

Impaired kidney function
In patients with mild to moderate renal function impairments, no dose reduction is necessary. (For patients with severe renal insufficiency, see section 4.3).

Impaired liver function (see section 5.2)
In patients with mild to moderate hepatic function impairments, no dose reduction is necessary. (For patients with severe hepatic dysfunction, see section 4.3).

Children and adolescents
The recommended daily dose for children and adolescents is up to 30mg/kg in divided doses and up to 10mg/kg in a single dose.
Children and adolescents below 12 years of age must not take **Ibufen 600**, as the active ingredient content is too high. For this age group, there are other ibuprofen preparations with lower concentrations of the active ingredient.

Method of administration

Ibufen 600 should be swallowed whole (not chewed) with adequate intake of liquid and not on an empty stomach. Patients with a sensitive stomach should take **Ibufen 600** with food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known hypersensitivity reactions (e.g. bronchospasm, asthma, rhinitis, urticaria or angioedema) after taking aspirin (acetylsalicylic acid) or other nonsteroidal anti-inflammatory drugs (NSAIDs) in the past.
- Unexplained blood disorders.
- Active or history of recurrent peptic ulcer or haemorrhage (at least 2 distinct episodes of confirmed ulceration or bleeding).
- History of gastrointestinal bleeding or perforation related to previous NSAID therapy.
- Cerebrovascular or other active bleeding.
- Severe liver or kidney impairment.
- Severe congestive heart failure (NYHA class IV).
- Severe dehydration (caused by e.g. vomiting, diarrhoea or insufficient consumption of liquid
- Last trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Undesirable effects may be minimized by using the lowest effective dose for the shortest possible duration to control symptoms (see section 4.2 and further below gastrointestinal and cardiovascular risks).

Gastrointestinal safety

Concomitant administration of **Ibufen 600** with NSAIDs, including cyclo-oxygenase-2 specific inhibitors, should be avoided.

Elderly patients:
With NSAID therapy, the elderly are at increased risk of adverse reactions, especially gastrointestinal bleeding and perforation, which may be fatal (see section 4.2).

Gastrointestinal bleeding, ulceration and perforation:
Gastrointestinal bleeding, ulceration or perforation, also 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 gastrointestinal effects.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment.
Caution should be advised in patients receiving concomitant medications which could increase the risk of ulcers or haemorrhage, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin re-uptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving **Ibufen 600**, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

<u>Cardiovascular and cerebrovascular effects</u>
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate decompensated heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trials suggest that use of ibuprofen, particularly at high doses (2,400 mg daily) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low doses of ibuprofen (e.g. ≤ 1,200 mg daily) are associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration, and high doses (2,400 mg daily) should be avoided.

Similar considerations should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), especially if high doses of ibuprofen (2,400 mg daily) are required.

Cases of Kounis syndrome have been reported in patients treated with this medicine. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Severe cutaneous adverse reactions (SCARs)
Serious cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of Ibuprofen (see section 4.8). Most of these reactions occurred within the first month. If signs and symptoms suggestive of these reactions appear, Ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

There have been exceptional cases of severe skin infections and soft tissue complications during varicella infection (see section 4.8). It is recommended to avoid **Ibufen 600** therapy during varicella infection.

Masking of symptoms of underlying infections
Ibufen 600 can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When **Ibufen 600** 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.

Also note:

Ibufen 600 must only be used after careful weighing of the benefit-risk-ratio
- With congenital impaired porphyrin metabolism (e.g. acute intermittent porphyria).
- With systemic lupus erythematosus (SLE) and mixed connective tissue disease (see section 4.8).

An especially careful medical supervision is necessary
- With a history of gastrointestinal disorders or with chronic inflammatory intestinal disorders (ulcerative colitis, Crohn's disease).
- With hypertension or congestive heart failure.
- With impaired renal function.
- With dehydration.
- With impaired hepatic function.
- Directly after major surgical procedures.

- With patients suffering from hay fever, nasal polyps or chronic obstructive respiratory diseases, as they are at increased risk of allergic reactions. These may be asthma attacks (so-called analgesic-induced asthma), Quincke's oedema or urticaria.
- With patients with allergic reactions to other substances, as they are also at higher risk of hypersensitivity reactions when using **Ibufen 600**.

Severe acute hypersensitivity reactions (e.g. anaphylactic shock) have been reported very rarely. **Ibufen 600** must be discontinued at the first appearance of hypersensitivity reactions after ingestion/use. Adequate therapeutic measures have to be taken by professionals.

Ibuprofen may temporarily inhibit platelet function (platelet aggregation). Patients with coagulation disorders should therefore be monitored closely.

In long-term use of **Ibufen 600**, liver function, kidney function and blood count should be checked regularly.

During prolonged use of painkillers, headaches may occur, which must not be treated by increasing the medicine dose.

In general, habitual intake of painkillers, especially a combination of several analgesic active ingredients, may permanently harm the kidneys with the risk of renal failure (analgesic nephropathy).

Concomitant use of NSAIDs and alcohol may worsen undesirable effects related to the active ingredient, especially those affecting the gastrointestinal tract or the central nervous system (CNS).

Regarding female fertility, see section 4.6.

Adolescents
There is a risk of renal impairment in dehydrated adolescents.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen (like other NSAIDs) should be used with caution in combination with:

Other NSAIDs including salicylates
Concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulceration and haemorrhage due to synergistic effects. Therefore, concomitant use of ibuprofen with other NSAIDs should be avoided (see section 4.4).

Aspirin (acetylsalicylic acid)
Due to the potential for increased undesirable effects, concomitant use of ibuprofen with aspirin is generally not recommended.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are administered concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, it cannot be

ruled out that regular long-term ibuprofen use can diminish the cardioprotective effect of low doses of aspirin. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Digoxin, phenytoin, lithium
Concomitant use of **Ibufen 600** with digoxin, phenytoin or lithium preparations may increase the serum level of these medicines. Surveillance of the serum lithium level is necessary, surveillance of the serum digoxin level and the serum phenytoin level is recommended.

Diuretics, ACE inhibitors, beta-adrenergic antagonists and angiotensin II receptor antagonists
NSAIDs may diminish the effect of diuretics and antihypertensive drugs. In patients with impaired renal function (e.g. dehydrated patients or elderly patients with impaired renal function), concomitant use of an ACE inhibitor, a *beta-blocker* or an angiotensin II receptor antagonist with a cyclooxygenase inhibitor may lead to further deterioration of the renal function, including a possibly acute renal failure, which is usually reversible. This combination should thus be chosen only with great caution, especially in elderly patients. Patients must be encouraged to an adequate intake of fluid and regular surveillance of renal parameters should be considered after initiation of a combination therapy.
Concomitant administration of **Ibufen 600** and potassium-sparing diuretics may cause hyperkalaemia.

Glucocorticoids
Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anti-platelet agents and selective serotonin re-uptake inhibitors (SSRIs)
Increased risk of gastrointestinal bleeding (see section 4.4).

Methotrexate
Administration of **Ibufen 600** within 24 hours before or after administration of methotrexate may lead to an increased methotrexate concentration and to an increase of its toxic effect.

Ciclosporin
Increased risk of nephrotoxicity of ciclosporin in concomitant use with certain NSAIDs. This effect cannot be ruled out either for a combination of ciclosporin with ibuprofen.

Anticoagulants
NSAIDs may enhance the effects of anticoagulants such as warfarin (see section 4.4).

Sulfonylurea
Clinical trials have shown interaction between NSAIDs and oral anti-diabetic medication (sulfonylurea). When Ibuprofen is used concomitantly with sulfonylurea, surveillance of blood glucose levels is recommended as a precaution.

Tacrolimus
Increased risk of nephrotoxicity when ibuprofen is administered with tacrolimus.

Zidovudine
There is evidence of an increased risk of haemarthroses and haematoma in HIV positive haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Probenecid and sulfinpyrazone
Medicinal products containing probenecid or sulfinpyrazone may retard ibuprofen excretion.

Quinolone antibiotics
Experimental data from animal studies suggest that NSAIDs may increase the risk of seizures associated with quinolone antibiotics. In patients receiving concomitant treatment with NSAIDs and quinolone, there may be an increased risk of developing seizures.

CYP2C9 inhibitors
Concomitant use of ibuprofen and CYP2C9 inhibitors may increase exposure to ibuprofen (CYP2C9 substrate). In a study involving voriconazole and fluconazole (CYP2C9 inhibitors), the exposure was approximately 80-100% higher compared to (S)-(+)-Ibuprofen. Reducing the ibuprofen dose 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
Ginkgo biloba may increase the NSAID-related risk of haemorrhage.

Mifepristone
NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

4.6 Fertility, pregnancy and lactation

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk of cardiovascular malformations increased from less than 1% to about 1.5%. It is assumed that the risk increases with increased dose and duration of therapy.

In animals, the administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation losses and embryo/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.

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.

- Use of NSAIDs, including **Ibufen 600**, at about 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.
- These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.
- There have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.
- Use of NSAIDs should be limited at 20 weeks gestation or later in pregnancy. If the NSAID effectiveness is considered to outweigh the risk to the foetus and the treatment is necessary at 20 weeks gestation or later, limit **Ibufen 600** use to the lowest effective dose and shortest duration possible.
- Consider ultrasound monitoring of amniotic fluid if **Ibufen 600** treatment at maximum daily dose extends beyond 5 days. Discontinue **Ibufen 600** if oligohydramnios or ductus arteriosus constriction occur and follow up according to clinical practice.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors

- may expose the foetus to:
  - cardiopulmonary toxicity (premature constriction / closure of the ductus arteriosus and pulmonary hypertension);
  - Renal dysfunction (see above);
- may expose the mother and the neonate at the end of pregnancy, to:
  - possible prolongation of bleeding time, an anti-aggregating effect which may occur even with very low doses.
  - inhibition of uterine contractions resulting in delayed or prolonged process of childbirth.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy.

Breast-feeding
The active ingredient ibuprofen and its metabolites pass into breast milk in low concentrations only. As adverse effects for the infant are not known, an interruption in lactation is usually not indicated during short-time use of ibuprofen. However, if a longer duration of treatment or higher doses are prescribed, early ablactation should be considered.

Fertility
The use of **Ibufen 600** may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of **Ibufen 600** should be considered.

4.7 Effects on ability to drive and use machines

Higher doses of **Ibufen 600** may cause adverse reactions affecting the central nervous system such as fatigue and dizziness, and can thus influence the capacity of response in individual cases and impair the ability to drive and to use machines. This is especially true in combination with alcohol.

4.8 Undesirable effects

Frequencies of undesirable effects are based on the following categories:

Very common	(≥ 1/10)
Common	(≥ 1/100 - < 1/10)
Uncommon	(≥ 1/1,000 - < 1/100)
Rare	(≥ 1/10,000 - < 1/1,000)
Very rare	(< 1/10,000)
Not known	(frequency cannot be estimated from the available data)

The following undesirable effects depend mainly on the dose and may vary individually; this has to be taken into account.

The most commonly observed undesirable effects are gastrointestinal in nature. Peptic ulcers, perforation or haemorrhage, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, digestive problems, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed. Especially the risk of gastrointestinal bleeding depends on the dose and the duration of treatment.

Oedema, hypertension and congestive heart failure have been reported in connection with NSAID therapy.

Clinical trials suggest that use of ibuprofen, particularly at high doses (2,400 mg daily) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Infections and infestations
Very rarely, worsening of infection-related inflammations (e.g. development of necrotizing fasciitis) has been reported simultaneously with systemic use of NSAIDs (including **Ibufen 600**). This may be connected to the effect mechanism of NSAIDs.

If during the treatment with **Ibufen 600** new infection signs occur or worsen, it is recommended that the patient consult a doctor immediately. It has to be verified whether a therapy with anti-infectives/antibiotics is indicated.

Very rarely, symptoms of aseptic meningitis with stiff neck, headache, nausea, vomiting, fever or disorientation have been reported during ibuprofen use. Patients with autoimmune disorders (SLE, mixed connective tissue disease) seem to be at increased risk.

Blood and lymphatic system disorders

Very rare: abnormal blood formation (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis).
Early signs may be: fever, sore throat, superficial lesions in the mouth, flue-like symptoms, strong exhaustion, nosebleed and ecchymosis.

In these cases, the patient should be instructed to immediately withdraw **Ibufen 600**, to avoid any self-medication using painkillers or fever-reducing medicines and to consult a physician.

In long-term therapy, the blood count should be checked regularly.

Immune system disorders
Uncommon: hypersensitivity reactions with skin rash and itching skin as well as asthma attacks (possibly with drop in blood pressure).

The patient must be instructed to immediately consult a doctor and to stop taking **Ibufen 600** in this case.

Very rare: severe general hypersensitivity reactions. They may be expressed as: facial oedema, tongue swelling, internal swelling of the larynx with restriction of the airways, difficulty in breathing, tachycardia, drop in blood pressure and even life-threatening shock.

With any of these signs, which can already appear at first intake of the medication, immediate medical attention is required.

Psychiatric disorders
Very rare: psychotic reactions, depression.

Nervous system disorders
Common: disturbances of the central nervous system such as headache, dizziness, insomnia, excitation, irritability or fatigue.

Eye disorders
Uncommon*:* visual impairment. In this case, the patient must be instructed to immediately consult a doctor and to stop taking **Ibufen 600.**

Ear and labyrinth disorders
Rare*:* tinnitus, hearing loss.

Cardiac disorders
Very rare: palpitations, oedema, cardiac insufficiency, cardiac infarction.
Not known: Kounis syndrome

Vascular disorders
Very rare: arterial hypertension.

Gastrointestinal disorders

Very common: gastrointestinal complaints like heartburn, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation and low gastrointestinal blood losses, which may cause anaemia in exceptional cases.
Common: gastrointestinal ulcers, possibly with bleeding and perforation, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4).
Uncommon: gastritis.
Very rare: oesophagitis, pancreatitis.

The patient must be instructed to stop taking the medication and to immediately consult a doctor if strong pain in the upper abdomen occurs or in case of melena or hematemesis.

Very rare: formation of intestinal, diaphragm-like strictures.

Hepatobiliary disorders
Very rare: liver dysfunction, liver damage, especially in long-term therapy, liver failure, acute hepatitis.

In long-term treatment, hepatic parameters should be checked regularly.

Skin and subcutaneous tissue disorders
Very rare: severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens–Johnson syndrome, and toxic epidermal necrolysis, alopecia.
Not known: drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis (AGEP), photosensitivity reactions.

There have been exceptional cases of severe skin infections and soft tissue complications during varicella infection (see "Infections and infestations ").

Renal and urinary disorders
Uncommon: formation of oedema, especially in patients with arterial hypertension or renal insufficiency, nephrotic syndrome; interstitial nephritis, which can accompany an acute renal failure.
Very rare: renal tissue lesions (papillary necrosis) and elevated uric acid concentration in the blood.

Renal function should be checked regularly.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

a) Symptoms of overdose

Possible symptoms are: nausea, stomachache, vomiting (possibly with blood), diarrhoea, headache, tinnitus, confusion, nystagmus, asthenia, dizziness, agitation, somnolence, drowsiness, disorientation, unconsciousness and seizures (especially in children also myoclonic seizures). Furthermore, gastrointestinal bleeding and liver or kidneys impairment, cold body feeling are possible. Prolonged use at higher than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia. In serious poisoning, metabolic acidosis may occur.
Hypothermia, hypotension, respiratory depression and cyanosis have also been reported. Further, the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Exacerbation of asthma is possible in asthmatics.

b) Treatment of intoxication
There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Non-steroidal anti-inflammatory drugs
Propionic acid derivatives
ATC code: M01AE01

Ibuprofen is a nonsteroidal anti-inflammatory drug, which has proved effective through its inhibitory effect on prostaglandin synthesis in the usual inflammation models in animal experiments. In humans, ibuprofen reduces pain, swelling and fever caused by inflammation. Ibuprofen also reversibly inhibits ADP-induced and collagen-induced platelet aggregation.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are administered concomitantly. In some pharmacodynamic studies, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate-release aspirin dosing (81 mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, it cannot be ruled out that regular long-term ibuprofen use can diminish the cardioprotective effect of low doses of aspirin. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Following oral application, ibuprofen is partly absorbed in the stomach and subsequently completely absorbed in the small intestine. After hepatic metabolization (hydroxylation, carboxylation), the pharmacologically inactive metabolites are excreted completely, mainly via the kidneys (90%), but also via the bile. In healthy people and in people with liver or kidney disease, the elimination half-life is 1.8 - 3.5 hours, the plasma protein binding is approximately 99%. Maximum plasma concentrations are reached 1 - 2 hours after oral administration of a normal-release dosage form.

5.3 Preclinical safety data

The subchronic and chronic toxicity of ibuprofen manifested in animal experiments mainly in form of lesions and ulcerations in the gastrointestinal tract.

In-vitro and *in-vivo* studies gave no clinically relevant indications to a mutagenic effect of ibuprofen. In studies with rats and mice, no indications for carcinogenic effects of ibuprofen were found.

Ibuprofen led to ovulation inhibition in rabbits as well as implantation disturbances in different animal species (rabbit, rat, mouse). Experimental studies in rats and rabbits showed that ibuprofen passes the placenta. Administration of maternally toxic doses led to increased occurrences of malformations (ventricular septal defect) in rat offspring.

Ibuprofen poses a risk to the biocoenosis in surface waters (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, maize starch, croscarmellose sodium, magnesium stearate, hypromellose, carmellose sodium, silica colloidal anhydrous, titanium dioxide (E171), stearic acid, talc, macrogol 400, carnauba wax.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a dry place, not above 25°C.

6.5 Nature and contents of container

Blister.

Pack size: 15, 30, 1000 caplets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicine poses a risk to the environment (see section 5.3).

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

7. MARKETING AUTHORISATION HOLDER

Dexcel Ltd.
1 Dexcel Street, Or Akiva, 3060000, Israel

8. MARKETING AUTHORISATION NUMBER

040 23 26009 00

Revised in October 2024 according to MOH guidelines.