PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

Imuran Tablets 25 mg, 50 mg

Each tablet contains: 25 mg or 50 mg Azathioprine.
For the list of inactive ingredients and allergens in the preparation – see section 2 **"Important information about some of the ingredients of this medicine"** and section 6 in the leaflet **"Additional information"**.

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

This medicine has been prescribed for your treatment. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Therapeutic activity: Immunosuppression.

This effect is important after an organ transplantation, so that the immune system will not reject the transplanted organ. Imuran is also used to treat rheumatoid arthritis that does not respond to other treatments – only by a rheumatologist in a hospital or clinic.

Therapeutic group: Immunosuppressants.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:
- You are sensitive (allergic) to the active ingredient azathioprine or to any of the other ingredients contained in the medicine (see section 6).
- You are sensitive (allergic) to mercaptopurine (a medicine similar to azathioprine, the active ingredient in Imuran).

Special warnings regarding use of the medicine
- **Before treatment with Imuran, tell the doctor if:**
  - You have recently received or are due to be vaccinated. During treatment with Imuran you should not be vaccinated with live vaccines (such as flu, measles, BCG, etc.) until the doctor confirms that this is safe for you, because some of the vaccines may cause infections during treatment with Imuran.
  - You have a genetic disorder known as Lesch-Nyhan Syndrome. This is a rare hereditary condition caused by a lack of an agent called HPRT (hypoxanthine-guanine-phosphoribosyltransferase).
  - You suffer from a liver or kidney disease.
  - You suffer from a syndrome called TPMT deficiency. This is a condition in which your body produces too little of an enzyme called TPMT (Thiopurine methyltransferase).
  - You have ever had chickenpox or shingles.
  - You have had hepatitis B (a liver infection caused by a virus).
  - You are due to have surgery, as some of the medicines, including tubocurarine or succinylcholine, that are given in surgery to relax muscles can affect the activity of Imuran. Inform the anesthesiologist if you are taking Imuran before the surgery.

If you are not sure if the above is relevant for you, consult your doctor, nurse or pharmacist before taking Imuran.

During treatment with Imuran, the doctor will instruct you to undergo **regular blood tests** to monitor changes in your condition (see section 3 **"How should you use the medicine?"**). The frequency of the tests will usually decrease as the treatment period lengthens.

If you are receiving immunosuppressive therapy, Imuran may increase your risk of:
- Tumors, including skin cancer. Therefore, during treatment with Imuran avoid long exposure to sunlight, wear protective clothing and use sunscreen with a high protective factor.
- White blood cell proliferation disorders (lymphoproliferative disorders):
  - Treatment with Imuran increases the risk of a certain type of cancer (lymphoproliferative disorder). When the treatment includes several immunosuppressants (including thiopurines), this may lead to death.
  - The combination of several immunosuppressants given concomitantly increases the risk of lymphatic system disorders due to viral infection (Epstein-Barr virus [EBV]-associated lymphoproliferative disorders).
- Development of a serious condition called Macrophage Activation Syndrome (excessive activation of white blood cells associated with inflammation processes), usually occurs in people who suffer from certain types of arthritis, severe chickenpox or shingles infection. Therefore, during treatment with Imuran, avoid contact with anyone suffering from chickenpox or shingles.
- If you have had hepatitis B in the past, the disease may become active again.
- Other infections, such as Progressive Multifocal Leukoencephalopathy (PML). Progressive Multifocal Leukoencephalopathy may occur in cases of a poor immune system. If there is a sign of infection, refer to the doctor (see section 4 **"Side effects"**).

Drug interactions

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, inform the doctor or pharmacist. This is because Imuran may affect the way some medicines work and other medicines may affect the way Imuran works. It is especially important to inform the doctor or pharmacist if you are taking or plan to take:
- Ribavirin, for treatment of viral infections.
- Methotrexate, mainly used to treat cancer.
- Allopurinol, oxipurinol, thiopurinol or other xanthine oxidase inhibitors, such as febuxostat, mainly used to treat gout.
- Penicillamine, mainly used to treat rheumatoid arthritis.
- ACE inhibitors, mainly used to treat hypertension.
- Anticoagulants, such as warfarin or acenocoumarol, for prevention of blood clots.
- Cimetidine, to treat stomach ulcers and indigestion.
- Indomethacin, used to relieve pain and anti-inflammatory.
- Cytostatic medicines to treat different types of cancer.
- Aminosalicylates, such as olsalazine, mesalazine or sulfasalazine mainly used to treat intestinal diseases called ulcerative colitis or Crohn's disease.
- Trimethoprim/sulfamethoxazole antibiotic, for the treatment of bacterial infections.
- Infliximab, mainly used to treat intestinal diseases called ulcerative colitis or Crohn's disease.
- Muscle relaxants, e.g., tubocurarine or succinylcholine, used during operations, as they may interact with Imuran Tablets. Before surgery, inform the anesthesiologist that you are being treated with azathioprine, since muscle relaxants given during anesthesia may interact with azathioprine.

If you are not sure if the above applies to you, consult with the doctor or the pharmacist before taking Imuran.

Vaccines during treatment with Imuran

Consult a doctor or nurse before receiving a vaccine. During treatment with Imuran you should not be vaccinated with live vaccines (such as vaccines for flu, measles, BCG, etc.) until the doctor confirms that this is safe for you. This is because some of the vaccines may cause infections during treatment with Imuran.

Use of the medicine and food

Do not take Imuran less than one hour before or less than three hours after food or drinking milk.

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may become pregnant or are planning to become pregnant, consult the doctor before commencing treatment with Imuran.

Pregnancy

Use reliable contraceptives to avoid pregnancy while you or your partner are taking Imuran.

If you are pregnant, your doctor will consider if you should take this medicine based on the risks and benefits of the treatment.

Breastfeeding

Small amounts of Imuran may pass into the breast milk. It is recommended that women taking Imuran avoid breastfeeding unless the benefits outweigh the potential risks to the child. Consult the doctor before breastfeeding.

Fertility

The effect of Imuran on fertility is unknown.

Driving and operating machinery

There is no known effect of taking Imuran tablets on the ability to drive or operate machines.

If you experience any side effect due to this medicine, be careful and if necessary, refrain from driving and using machines.

Important information about some of the ingredients of this medicine

The tablets contain lactose monohydrate. If you have been told that you have an intolerance to certain sugars, inform the doctor before commencing treatment with Imuran.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are unsure about the dosage and treatment regimen of the preparation.

The dosage and treatment regimen will be determined by the doctor only, in accordance with the severity of your disease, age, weight and kidney and liver functions.

The elderly or patients with a kidney or liver disease may need lower dosages.

Take the tablet with a little water.

Do not halve, break or crush the tablet.

The product is cytotoxic.

Do not exceed the recommended dose.

If you have accidentally taken a higher dosage

If you took an overdose or if a child or anyone else accidentally swallowed the medicine, immediately refer to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

The immediate signs of overdose are: nausea, vomiting and diarrhea, low white blood cell count, unexplained infection, throat ulcer, bleeding and bruising.

If you forgot to take the medicine

If you forgot to take the medicine at the designated time, do not take a double dose. If it is almost time for the next dose, take the next dose at the regular time and consult the doctor. If not, take the tablet as soon as you remember and continue treatment as required.

If you stop taking the medicine

Adhere to the treatment regimen as recommended by the doctor. Even if there is an improvement in your health, do not discontinue or change the manner of treatment with the medicine without consulting the doctor.

Tests and follow-up

During the course of treatment with this medicine, and afterwards, be sure to perform blood tests – in the first eight weeks of taking the medicine, weekly blood tests should be performed.

When using a high dosage or if there is liver or kidney failure, perform blood tests more frequently. Afterwards, perform blood tests once a month or at least once in three months.

Perform liver function tests in patients with impaired liver function.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take medicine. Wear glasses if you need them.

If you have further questions regarding use of this medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Imuran 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.

Discontinue treatment and refer to the doctor immediately if you notice the following serious side effects; there may be a need for urgent medical care:
- Allergic reactions (uncommon side effects may appear in up to one out of 100 users); the signs may include:
  - General tiredness, dizziness, nausea, vomiting, diarrhea or abdominal pain
  - Swelling of the eyelids, face, or lips
  - Redness of the skin, skin lesions or skin rash (including blisters, itching and skin peeling)
  - Muscle or joint pain
  - Sudden appearance of wheezing, coughing or breathing difficulties

  In severe cases the reaction can be life-threatening (rare, may appear in up to one out of 10,000 users).
- Skin redness or rash that may develop into a life-threatening skin reaction that includes a widespread rash with blisters and skin peeling, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome), extensive peeling of the skin (toxic epidermal necrolysis) (these are very rare side effects that may appear in up to one out of 10,000 users).
- Reversible pneumonia (causes shortness of breath, coughing and fever) (a very rare side effect that may appear in up to one out of 10,000 users).
- Blood and bone marrow disorders; the signs will include: weakness, tiredness, paleness, bruising easily, unusual bleeding or infections (very common side effects that may appear in more than one out of 10 users).
- When Imuran is used for treatment in combination with other immunosuppressives, you are at risk of a viral disease that harms the brain. The signs can be: headaches, changes in behavior, speech impairment, a decrease in cognitive abilities, such as memory, concentration and decision-making (cognitive decline). This condition (called JC virus-associated Progressive Multifocal Leukoencephalopathy) may be fatal (a very rare side effect that may appear in more than one out of 10,000 users).

Refer to the attending doctor or a specialist immediately if you notice the following serious side effects, there may be a need for urgent medical care:
- You have a fever or any other sign of infection, such as sore throat, sore mouth, urinary problems, or respiratory system infections that cause shortness of breath and coughing (very common side effects – may appear in more than one out of 10 users).
- Problems in your liver; the signs include yellowing of the skin and the whites of the eye (jaundice) (an uncommon side effect that may appear in up to one out of 100 users).
- Various types of cancer, such as blood, lymph and skin cancer (see section 2 **"Special warnings regarding use of the medicine"**) (rare side effects – may appear in up to one out of 1,000 users).
- Sweet's syndrome, also called *acute febrile neutrophilic dermatosis*. You may develop a rash (raised red, with pink or purple lumps and sore to the touch), particularly in the area of the arms, hands, fingers, neck and face, may be accompanied by fever (side effect whose frequency is unknown [not yet determined]).
- A certain type of lymphoma (*hepatosplenic T-cell lymphoma*). You may develop nose bleeds, fatigue, significant night sweats, weight loss, and unexplained high fever (side effect whose frequency is unknown [not yet determined]).

Discontinue treatment immediately and refer to the doctor if you notice the side effects listed above.

Additional side effects

Very common side effects – appear in more than one out of 10 users
- Low level of white blood cells in blood tests, which may cause an infection.

Common side effects – appear in up to one out of 10 users
- Nausea.

Uncommon side effects – appear in up to one out of 100 users
- Anemia, low red blood cell level.
- Inflammation of the pancreas (pancreatitis) that may cause severe pain in the upper abdomen.

Rare side effects – appear in up to one out of 1,000 users
- You may notice hair loss while taking Imuran. The hair will often grow again despite continuing treatment with the medicine. If you are worried, consult the doctor.

Very rare side effects – appear in up to one out of 10,000 users
- Intestinal damage, which may cause diarrhea, abdominal pain, constipation, nausea and vomiting (can indicate bowel perforation).

Side effects whose frequency is unknown (not yet determined)
- Photosensitivity (sensitivity to sunlight and any other light).
- You may develop a rash (raised red, with pink or purple lumps and painful to the touch), particularly in the area of the arms, hands, fingers, neck and face, may be accompanied by a fever (Sweet's syndrome, also called acute febrile neutrophilic dermatosis).

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

<u>Reporting side effects</u>:

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (<u>www.health.gov.il</u>) that directs you to the online form for reporting side effects, or by entering the link: <u>https://sideeffects.health.gov.il</u>

In addition, you can report to the company via the following address:

<u>Padagis.co.il</u>

5. HOW SHOULD THE MEDICINE BE STORED?
- Avoid poisoning! This medicine and any other medicine must be kept in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting without explicit instruction from the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package and blister. The expiry date refers to the last day of that month.
- Store below 25°C. Protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your 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, the medicine also contains:

Lactose monohydrate, maize starch, pregelatinised starch, magnesium stearate, stearic acid.

The Imuran 25 mg tablet coating contains:

Opadry Orange 06B230003 (hypromellose, titanium dioxide, macrogol 400, iron oxide yellow, iron oxide red).

The Imuran 50 mg tablet coating contains:

Hypromellose, macrogol 400.
- **What the medicine looks like and contents of the package:**

  The Imuran 25 mg tablet is an orange, round, biconvex, unscored tablet marked with IM 2.

  The Imuran 50 mg tablet is a yellow, round, biconvex, scored tablet marked with IM 5.

  The tablets come in blister packages. Each package contains 100 tablets.
- Registration holder: Padagis Israel Agencies Ltd., 1 Rakefet St., Shoham.
- Manufacturer: Aspen Pharma Trading Ltd., Dublin, Ireland.
- Revised in March 2023 according to MOH guidelines.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
  Imuran 25 mg tablets: 3479.25384
  Imuran 50 mg tablets: 4265.22964

03.2023