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

The medicine is dispensed with a doctor's prescription only

Puri-Nethol Tablets 50 mg

Each tablet contains mercaptopurine 50 mg

Inactive ingredients and allergens in the preparation: see section 2 **"Important information about some of the ingredients of the medicine"** and section 6 in the leaflet **"Further information"**.

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

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

1. WHAT IS THE MEDICINE INTENDED FOR?

Puri-Nethol is used to treat various types of leukemia.

Therapeutic group: Cytotoxic immunosuppressive medicines, purine analogues.

2. BEFORE USING THE MEDICINE

Do not use the medicine:

- if you are sensitive (allergic) to the active ingredient or to any of the additional ingredients contained in the medicine (see section 6).
- if you are breastfeeding.
- you should not be vaccinated with the yellow fever vaccine while taking Puri-Nethol, as it may be lethal.

Special warnings regarding use of the medicine

Before treatment with Puri-Nethol, tell the doctor if:

- You were recently vaccinated or are about to be vaccinated. If you have been vaccinated with the yellow fever vaccine.
- You take Puri-Nethol, you should not have a live vaccine (such as: flu, measles, BCG vaccines, etc.) until the doctor confirms that this is safe for you. This is because certain vaccines may cause infection if you receive them during treatment with Puri-Nethol.
- You have kidney or liver problems, since your doctor will have to check that they are functioning properly.
- You have a condition in which your body produces amounts of an enzyme called TPMT (thiopurine methyltransferase) that are too low, as your doctor may have to adjust the dosage.
- You are planning to have a baby. This warning applies to both men and women. Puri-Nethol may harm your sperm or eggs (see **"Pregnancy, breastfeeding and fertility"** section in the leaflet).
- You have a sensitivity (allergy) to a medicine called Imuran (azathioprine) (also used to treat cancer).
- You have, or have not, had chickenpox, shingles or hepatitis B (a liver disease caused by a virus).
- You have a genetic disorder called Lesch-Nyhan Syndrome.

If you are receiving treatment to suppress the immune system, taking Puri-Nethol may increase your risk for:

- Tumors, including skin cancer. Therefore, during treatment with the medicine, avoid prolonged exposure to sunlight, wear protective clothing and use sunscreen with a high protection factor.
- Lymphoproliferative disorders:
  - Treatment with Puri-Nethol increases your risk for a certain type of cancer called lymphoproliferative disorder. When the treatment includes a number of immunosuppressive medicines (including thiopurines), this condition may lead to death.
  - A combination of multiple immunosuppressive medicines, given concomitantly, increases the risk for lymphatic system disorders due to a viral infection [Epstein-Barr virus (EBV)-associated lymphoproliferative disorders].

Taking Puri-Nethol may increase your risk for:

- Developing a severe condition called Macrophage Activation Syndrome (hyperactivation of white blood cells related to inflammation processes), which usually occurs in people suffering from certain types of arthritis.
- Some patients with inflammatory bowel disease who received Puri-Nethol developed a rare and aggressive type of cancer called Hepatosplenic T-cell Lymphoma (see section 4 "**Side effects**").

Use of Puri-Nethol for the treatment of inflammatory bowel disease (IBD) is an unlicensed indication.

Infections

When you are treated with Puri-Nethol, the risk of a viral, fungal and bacterial infections is increased, and the infections can be more serious. See also section 4 **"Side effects".**

Tell your doctor before starting treatment whether or not you have had chickenpox, shingles or hepatitis B (a liver disease caused by a virus).

Children and adolescents

Low blood sugar values (sweating more than usual, nausea, dizziness, confusion, etc.) have sometimes been observed in children, primarily in children under 6 years of age or who have a low body weight.

Talk to your child's doctor if this occurs.

Blood tests

Treatment with Puri-Nethol may affect your bone marrow. This means that you may have a lower number of white blood cells, platelets and red blood cells (less common) in your blood. At the beginning of the treatment, the doctor will refer you to do daily blood tests, and at least a weekly test during the treatment, this is in order to monitor the levels of these cells in your blood. If you stop the treatment early enough, the blood cell levels will return to normal values.

Liver function

Puri-Nethol has a toxic effect on your liver. Therefore, the doctor will refer you for weekly liver function tests during treatment with Puri-Nethol. If you have a liver disease or if you are taking other medicines that can have an effect on your liver, the frequency of the tests will increase. If you notice yellowing of the whites of the eyes or of the skin (jaundice), report this to the doctor immediately, as it may be necessary to immediately stop treatment with Puri-Nethol.

Pellagra [a disease caused by extreme niacin (nicotinic acid) deficiency in the cells of the body]

Talk to your doctor immediately if you experience diarrhea, localized pigmented rash (dermatitis), decline in your memory, reasoning or other thinking skills (dementia), as these symptoms may suggest vitamin B3 deficiency (nicotinic acid deficiency/ pellagra). Your doctor will likely prescribe vitamin supplements (niacin/nicotinamide) for you to help treat this condition.

Sun and UV light

While you are taking Puri-Nethol, you are more sensitive to the sun and UV light. You must make sure to limit your exposure to the sunlight and UV light, wear protective clothing and use a sunscreen with a high sun protection factor.

If you are not sure whether the above applies to you, refer to the doctor or pharmacist before taking Puri-Nethol.

Drug interactions

If you are taking, or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Especially if you are taking:

- Ribavirin (to treat viral infections).
- Other cytotoxic medicines (chemotherapy to treat cancer).
- Allopurinol, thiopurinol, oxypurinol or febuxostat (to treat gout).
- Olsalazine or mesalazine (to treat Crohn's disease and an intestinal problem called ulcerative colitis).
- Sulfasalazine (to treat rheumatoid arthritis or ulcerative colitis).
- Methotrexate (to treat rheumatoid arthritis or severe psoriasis).
- Infliximab (to treat Crohn's disease and ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis or severe psoriasis).
- Warfarin or acenocoumarol – anticoagulants (to thin the blood).
- Anti-epileptic medicines such as phenytoin, carbamazepine. Blood levels of anti-epileptic medicines may need to be monitored and their dosages adjusted, if necessary.

Use of vaccines while taking Puri-Nethol

If you are due to be vaccinated, consult first with the doctor or nurse. When you are taking Puri-Nethol, do not get vaccinated with a live vaccine (e.g., polio, measles, mumps and rubella) until the doctor confirms that this is safe for you, as certain vaccines may cause an infection if you receive them during treatment with Puri-Nethol.

Use of the medicine and food

See section 3 **"How should you use the medicine?"**.

Pregnancy, breastfeeding and fertility

If you are planning to have a baby, do not take Puri-Nethol without first consulting your doctor. This warning applies to both men and women. Puri-Nethol may harm your sperm or eggs.

Reliable contraception must be used to avoid pregnancy whilst you or your partner are taking Puri-Nethol. Both men and women should continue to use effective contraception for at least 3 months after stopping treatment. If you are already pregnant, you must talk to your doctor before taking Puri-Nethol. Women who are pregnant or who are planning to be pregnant or who are breastfeeding should not come into contact with Puri-Nethol preparation. Do not breastfeed while taking Puri-Nethol. Consult your doctor, pharmacist or midwife.

Driving and operating machinery

Puri-Nethol is not expected to affect your ability to drive or operate machinery, but no studies have been performed to confirm this.

Important information about some of the ingredients of the medicine

Puri-Nethol tablets contain lactose. If the doctor has told you that you are sensitive to certain sugars, refer to the doctor before using the medicine.

3. HOW SHOULD YOU USE THE MEDICINE?

Puri-Nethol should only be given to you on the instruction of a doctor who specializes in treating blood diseases.

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

The dosage and treatment regimen will be determined by the doctor only. The dosage will be determined individually and depends on other treatments being given to the patient. It is important to be sure to take the medicine at designated times.

- Take the medicine at least one hour before or 3 hours after food or drinking milk.
- Swallow the medicine whole with a glass of water.
- **The score line on the tablet is not intended for halving the tablet.** It is not recommended to halve, crush or chew the tablets.

The product is cytotoxic.

If you or your caregiver come into contact with broken tablets, wash the hands immediately.

Tests and follow-up

During the course of treatment with Puri-Nethol, the doctor will perform routine blood tests. This is to check your blood cell count and liver function.

The doctor may perform other blood and urine tests to monitor uric acid level, which can rise during treatment with Puri-Nethol. The doctor may change the dosage during treatment in accordance with the test results.

- In adult patients – the dosage may be reduced in accordance with the results of kidney and liver functions.
- In patients with kidney or liver problems – the dosage may be reduced.
- If you have a TPMT enzyme deficiency – the dosage may be reduced.

Do not exceed the recommended dose.

If you accidentally take a higher dosage

If you have taken an overdose you may feel nauseous, vomit or have diarrhea. If you have taken an overdose or if a child or anyone else has accidentally swallowed the medicine, refer immediately to the doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forget to take the medicine

If you forgot to take this medicine at the designated time, tell the attending doctor. **Do not take a double dose to compensate for a forgotten dose.**

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 stop the treatment with the medicine without consulting the doctor.

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

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

4. SIDE EFFECTS

As with any medicine, use of Puri-Nethol 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.

Refer immediately to your specialist doctor or the hospital if any of the following symptoms appears:

- An allergic reaction – signs may include:
  - Skin rashes
  - High fever
  - Joint pain
  - Swollen face
  - Any signs of fever or infection (sore throat, sore mouth or urinary problems).
  - Any unexpected bruising or bleeding, as this could indicate low production of blood cells of a particular type.
  - If you suddenly feel unwell (even if your body temperature is normal) and have abdominal pain and nausea, as this could be a sign of an inflamed pancreas.
  - Yellowing of the whites of the eyes or skin (jaundice)
  - Skin nodules (erythema nodosum) (frequency unknown).

Consult the doctor if you have one of the following side effects which may occur with this preparation:

Very common side effects – occur in more than one in ten users

- A drop in the number of white blood cells and platelets (may show up in blood tests)

Common side effects – occur in 1-10 in 100 users

- Nausea or vomiting
- Liver damage – may show up in blood tests
- A drop in the number of red blood cells which may make you tired, weak or breathless (called anemia)
- Loss of appetite
- Inflammation of the mouth (stomatitis)
- Pancreatitis in patients with inflammatory bowel disease

Uncommon side effects – occur in 1-10 in 1,000 users

- Joint pain
- Skin rash
- Fever
- Irreversible damage to the liver (hepatic necrosis)
- Bacterial and viral infections, infections associated with neutropenia (atypical reduction in the number of white blood cells in the circulation)

Rare side effects – occur in 1-10 in 10,000 users

- Hair loss
- Mouth ulcers
- In men: temporary low sperm count
- Allergic reaction which results in swollen face
- Various types of cancer including blood, lymph and skin cancer
- Pancreatitis in patients with cancer of the blood (leukemia)

Very rare side effects – occur in less than one in 10,000 users

- A different type of leukemia than that which is being treated
- Ulcers in the intestines; symptoms may include abdominal pain and bleeding

Side effects whose frequency is unknown (not yet determined)

- A rare type of cancer – Hepatosplenic T-cell Lymphoma, in patients with a condition called inflammatory bowel disease (see section 2 **"Special warnings regarding use of the medicine"**)
- Increased sensitivity to sunlight and UV light causing skin reactions
- Pellagra (vitamin B3 – niacin deficiency) associated with pigmented rash; diarrhea or memory loss
- Decreased blood sugar levels

Additional side effects in children

Low blood sugar levels (sweating more than usual, nausea, dizziness, confusion, etc.) have been reported in some children taking Puri-Nethol. The frequency of this effect is not known; however, most of the children were under the age of 6 years and had a low body weight.

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.

Reporting of side effects:

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 (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

Additionally, you can report to Padagis company via the following address: Padagis.co.il

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine, and any other medicine, should be stored in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the carton package and the bottle label. The expiry date refers to the last day of that month.
- Store below 25°C, in a dry place. Keep the bottle tightly closed.
- If your doctor instructs you to stop treatment, it is important to return all remaining medicine to the pharmacist so that he/she can dispose of it according to the guidelines for disposal of dangerous substances. Only keep the remainder of the medicine with you upon specific instruction from the doctor.

6. FURTHER INFORMATION

- **In addition to the active ingredient, the medicine also contains:**
  Lactose monohydrate, maize starch, modified maize starch, magnesium stearate, stearic acid.
- **What the medicine looks like and contents of the package:** Round and convex, pale yellow tablets, with a line (which is not used for halving) on one side, where PT is marked above the line and 50 is marked below it, with no marking on the other side, in a glass bottle containing 25 tablets.
- **Registration holder and address:** Padagis Israel Agencies Ltd., 1 Rakefet St., Shoham.
- **Manufacturer and address:** Aspen Pharma Trading Ltd., Dublin, Ireland.
- Revised in September 2023 according to MOH guidelines.
- Registration number of the medicine in the National Medicines Registry of the Ministry of Health: 3344.22532