Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Hydroxyurea medac 500 mg
Capsules

Active ingredient
Each capsule contains:
hydroxycarbamide 500 mg

Inactive ingredients and allergens: See section 2 "Important information about some of this medicine's ingredients" and section 6 "Additional information".

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your 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 it seems to you that their illness is similar to yours.

1. What is this medicine intended for?
Hydroxyurea Medac is indicated for the treatment of patients with chronic myeloid leukemia (CML) in the chronic or accelerated phase of the disease.
Hydroxyurea Medac is also indicated for the treatment of patients with essential thrombocythemia or polycythemia vera with a high risk of thromboembolic complications.

Therapeutic group: Hydroxyurea Medac contains the active ingredient hydroxycarbamide, which belongs to the group of medicines used in certain blood diseases and interfering with the growth of cancer cells.

2. Before using this medicine
Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient (hydroxycarbamide) or to any of the other ingredients in this medicine (see section 6 "Additional information"). Stop the treatment if hypersensitivity to Hydroxyurea Medac occurs.
- The blood cell count is too low.

Special warnings about using this medicine
- Treatment with hydroxycarbamide requires comprehensive observation (see section "Tests and follow-up").
- You should drink plenty of liquids during the treatment.
- Secondary leukemia may develop due to long-term treatment with hydroxycarbamide. It is currently unknown to what extent this results from the underlying disease or from treatment with hydroxycarbamide.
- Skin cancer has been reported in patients who received long-term treatment with hydroxycarbamide. You should protect your skin from sunlight and regularly perform self-examinations of your skin during the treatment and after discontinuing treatment with hydroxycarbamide. Your doctor will also examine your skin during routine follow-up visits.

- You may suffer from leg ulcers. In such case, your doctor will decide if you should continue taking this medicine. The ulcers usually heal slowly over several weeks, if you stop taking this medicine.
- Previous or concomitant radiation may cause skin redness and irritation.

Before treatment with Hydroxyurea Medac, tell your doctor:
- If you have ever suffered from gout and/or you have folic acid deficiency.
- If you have a decrease in red blood cell counts (anemia) before the treatment or you have developed it during the treatment, red blood cells can be replaced if required. If hemolytic anemia (a disorder in which red blood cells are destroyed more rapidly than they are produced) is discovered in blood tests, your doctor will stop the treatment with Hydroxyurea Medac.
- If you have kidney and/or liver problems.

Children and adolescents
This medicine is not intended for children and adolescents under the age of 18 years. There is no information regarding the safety and efficacy of using this medicine in children and adolescents under the age of 18 years.

Tests and follow-up
Before and during the treatment, blood tests will be done for you to check that you have enough blood cells and sufficient kidney and liver functions to receive this medicine. Blood tests will be usually performed once a week.

Drug interactions
If you are taking, or have recently taken, or may take other medicines, including non-prescription medications and dietary supplements, tell your doctor or pharmacist.

Important aspects related to the use of this medicine together with other medicines or treatments:
- If you have previously received or still receiving any similar medicines or radiotherapy, side effects may be more frequent and more serious. These effects include mainly decrease in blood cell number (myelosuppression), inflammation of gastric mucosa and dermatitis.
- Hydroxycarbamide may enhance the activity of NRTI (nucleoside reverse transcriptase inhibitors), which are medicines used to treat HIV (e.g. didanosine, stavudine). Hydroxycarbamide in combination with didanosine, stavudine, and indinavir has been shown to cause a decrease in white cell counts (CD4 lymphocytes decreased). Combination of hydroxycarbamide with NRTI may increase the risk of side effects of NRTI.
- If you have been recently vaccinated or plan to receive a vaccine, tell your doctor.

Using this medicine and food
This medicine can be taken with or without food.

Pregnancy, breastfeeding, and fertility
If you are pregnant or breastfeeding, think that you are pregnant or plan to become pregnant, consult your doctor or pharmacist before taking this medicine.

<u>Pregnancy</u>
There is a risk of harmful effects on the developing baby. Therefore, do not take this medicine during pregnancy, unless this has been explicitly determined by your doctor.

You must use effective contraceptives before starting treatment, during the treatment and for 6 months after treatment with this medicine. If you become pregnant during or after taking the medicine, contact your doctor.

Breastfeeding
Do not take Hydroxyurea Medac while breastfeeding, unless this has been explicitly determined by your doctor. The active ingredient of Hydroxyurea Medac passes into breast milk.

Fertility
During the treatment and for 3 months after treatment discontinuation, men are advised to use effective contraceptives. Ask your doctor about the possibility of sperm preservation before starting the first treatment.
Genetic counselling is recommended for patients intending to have children after therapy.

Driving and using machines
The ability to react may be impaired during treatment with Hydroxyurea Medac. You should remember this when increased attention is required, for example, while driving and using machines.

Important information about some of this medicine's ingredients
This medicine contains lactose
If you have been told by your doctor that you have an intolerance to certain sugars, contact your doctor before taking this medicine.

This medicine contains sodium
This medicine contains less than 1 mmol (23 mg) sodium per capsule, that is, it is essentially "sodium-free".

3. How to use this medicine?
Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine. Only your doctor will determine your dose and how you should take this medicine.

The recommended dosage is usually:
Adults
For chronic myeloid leukemia, the common initial dosage is 40 mg/kg body weight, daily. Subsequently, the dosage is adjusted individually in accordance with the white blood cell count.

For polycythemia vera, the common initial dosage is 15-20 mg/kg body weight, daily. Subsequently, the dosage is adjusted individually to 1-2 capsules (500-1,000 mg) in accordance with the blood cell count.

For essential thrombocythemia, the common initial dosage is 15 mg/kg body weight, daily, with individual dosage adjustment in accordance with the blood cell count.

Elderly patients
Elderly patients may be more sensitive to hydroxycarbamide and may need a lower dosage.
Do not exceed the recommended dose.

Mode of administration
- Swallow the capsules whole and do not let them degrade in the mouth. Do not open the capsule and do not disperse its content.

- Handle the capsules carefully. Use gloves or wash your hands thoroughly after handling them.
- Even if the risks to the fetus are minimal, pregnant women should refrain from handling the capsules.

If you have accidentally taken a higher dose, inform your doctor immediately.
If you have taken a higher dose of the medicine than the one prescribed for you, always contact a doctor or go to a hospital. You may experience symptoms affecting the mucous membranes and the skin.
If you have taken an overdose or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take this medicine
It is important to follow the course of treatment exactly as prescribed by your doctor.
Do not take a double dose to compensate for a forgotten dose.
If you have missed one dose, continue with the treatment as prescribed. If you have missed several doses, continue with the treatment as prescribed, but contact your doctor for additional advice.

Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop treatment with this medicine without consulting your doctor.

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

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects
Like with all medicines, using Hydroxyurea Medac may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Contact your doctor immediately if you experience symptoms such as:
- Fever, cough or respiratory problems, may be signs of a serious lung disease (unknown incidence)
- High fever (above 39°C) accompanied by stomach, lung, muscle, liver, skin and heart problems within 6 weeks of taking Hydroxyurea Medac (incidence: rare)

Very common side effects (may affect more than 1 in 10 users):
- Lack of sperm or low quantity of sperm in semen (azoospermia or oligospermia)
- Decrease in blood cell number (myelosuppression), especially white blood cells (leukocytopenia), including a type of white blood cell that helps the body to fight the disease (decrease in CD4 lymphocytes), red blood cells (anemia), and platelets (thrombocytopenia)
- Nausea, vomiting, loss of appetite, sores in the mouth (stomatitis), diarrhea, constipation, abdominal pain, inflammation of gastrointestinal mucosa (mucositis), dyspepsia
- Black tarry stool or blood in stool
- In combination with certain HIV treatments: pancreatitis with gastric or abdominal pain
- Drug-induced fever, chills, a feeling of discomfort, weakness, asthenia
- Skin ulcers, especially leg ulcers

- Skin eruptions manifested by spots or blisters (maculopapular rash), facial redness, redness in hands and feet (hand and foot syndrome)
- Skin changes such as purple rash and skin thinning; darkening and atrophy of nails and skin, purple, small and itchy skin papules; skin peeling (scaling), blackening and death of skin
- Hair loss (alopecia)
- Temporary kidney problems with an elevation of certain blood parameters such as uric acid, urea and creatinine
- Difficulties urinating

Common side effects (may affect up to 1 in 10 users):
- Enlarged immature red blood cells (megaloblastosis)
- Skin cancer
- Elevated liver enzymes
- Hepatitis causing flu-like symptoms, including fatigue, loss of appetite, fever, pain and nausea/vomiting, pressure or pain below the right ribs and may also include yellowing of the skin or eyes
- Problems with bile flow (cholestasis). Bile produced by the liver to assist in food digestion may not flow properly. Bile accumulation may cause itching, yellow skin, very dark urine, and very pale stool
- Neurological disorders including headaches, dizziness, somnolence, disorientation, hallucinations, and seizures
- Acute and chronic lung reactions, with changes in the lung tissue visible on X-ray imaging and shortness of breath, as well as fever in acute reactions and dry cough in chronic reactions
- In combination with certain HIV treatments: numbness and tingling, or pain in the arms and legs (peripheral neuropathy) and abdominal pain, nausea or vomiting, or yellow skin (hepatotoxicity)

Uncommon side effects (may affect up to 1 in 100 users):
- Thick and scaly skin patches (actinic keratosis)
- High levels of red blood cell degradation products (bilirubin) in blood

Rare side effects (may affect up to 1 in 1,000 users):
- Allergic reactions
- Metabolic complications due to degradation products of cancer cells (tumor lysis syndrome)
- Skin ulcer with severe infection

Very rare side effects (may affect up to 1 in 10,000 users):
- Dermatitis causing red scaly patches that can occur in combination with joint pain
- Reduced kidney function

Side effects of unknown frequency (the frequency cannot be estimated from the existing information):
- High blood levels of potassium, which may cause abnormal heart rate
- Fever, cough or respiratory problems, may be signs of a serious lung disease; inflammation of air sacs due to an allergic reaction
- Hemolytic anemia
- Dry skin

Cases of low sodium levels, which may cause fatigue and confusion, muscle cramps, seizures or coma, have been observed in post-marketing follow-up.

Secondary leukemia (blood cancer) may develop if you are receiving long-term treatment with hydroxycarbamide. It is currently unknown to what extent this results from the underlying disease or from treatment with hydroxycarbamide.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects
You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link:
https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.
- Store below 25˚C.
- Do not throw away any medicines via wastewater or household waste. Ask the pharmacist how to dispose of 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:

Capsule content:
disodium citrate, lactose monohydrate, calcium citrate, magnesium stearate

Capsule coating:
gelatin, titanium dioxide (E171)

What the medicine looks like and contents of the pack:
White gelatin capsules, filled with an off-white powder.
Available in packs of 100 capsules.

Registration holder's name and address:
Tzamal Bio-Pharma Ltd., 20 Hamagshimim St., Kiryat Matalon, Petach Tikva.

Manufacturer's name and address:
Medac Gesellschaft für klinische Spezialpräparate mbH., Theaterstrasse 6, 22880, Wedel, Germany.

This leaflet was revised in June 2023 according to MOH guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 168-84-35373-00

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