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

The 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 in the preparation: see section 2 "Important information about some of the ingredients of the medicine" and section 6 "Additional information".

Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have any other questions, refer to the doctor or the pharmacist.
This medicine has been prescribed for treatment of your illness. Do not pass it on to others. It may harm them even if it seems to you that their illness is similar.

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

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

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

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

Special warnings regarding the use of the medicine
- Treatment with hydroxycarbamide requires extensive supervision (see "Tests and follow-up" section).
- You should drink plenty of fluids during the treatment.
- Secondary leukemia may develop due to long-term treatment with hydroxycarbamide. It is currently not known to what extent this results from the underlying disease or from treatment with hydroxycarbamide.
- Skin cancer has been reported in patients receiving hydroxycarbamide over a long period of time. You should protect your skin from the sun and regularly check your skin yourself during treatment and after discontinuing treatment with hydroxycarbamide. The doctor will also check your skin during routine follow-up visits.
- You may have leg ulcers. In this case, the doctor will decide whether you should continue taking this medicine. The ulcers usually heal slowly over a number of weeks, if you stop taking this medicine.
- Previous or concomitant radiation may cause redness and irritation of the skin.

Before treatment with Hydroxyurea medac inform the doctor:
- If you have ever suffered from gout and/or if you have folic acid deficiency.
- If you have a decrease in red blood cell counts (anemia) before treatment or if you develop it during treatment, red blood cells can be replaced if necessary. If hemolytic anemia (a disorder in which red blood cells are destroyed faster than they are made) is detected during blood tests, the doctor will discontinue treatment with Hydroxyurea medac.
- If you suffer from kidney and/or liver problems.
- If you suffer from diabetes and use a continuous glucose monitor (CGM) to check the level of glucose in your blood. Hydroxycarbamide (also known as hydroxyurea) may cause falsely high sensor glucose values from certain sensors. This may result in using higher amounts of insulin than needed, leading to low blood sugar level (hypoglycemia). Talk to the doctor who instructed you to use a continuous glucose monitor (CGM) regarding the safety of using it while taking Hydroxyurea medac.

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

Tests and follow-up
You will have blood tests before and during treatment, in order to check that you have enough blood cells and sufficient kidney and liver function to receive this medicine. Blood tests will usually be performed once a week.

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

Important points regarding the use of this medicine together with other medicines or treatments:
- If you have previously received or are still receiving any similar medicines or radiation therapy, side effects can be more frequent and more severe. These effects mainly include a decrease in blood cell count (suppression of bone marrow function), inflammation in the mucous membrane of the stomach and skin inflammation.
- Hydroxycarbamide may increase the activity of NRTI (nucleoside reverse transcriptase inhibitors), which are medicines used for treatment of HIV (for example, didanosine, stavudine). Hydroxycarbamide in combination with didanosine, stavudine and indinavir have caused a decrease in white cell count (a decrease in CD4 lymphocytes). The combination of hydroxycarbamide with NRTI may increase the risk of NRTI side effects.
- If you have recently been vaccinated or if you plan to get a vaccine, tell your doctor about this.

Use of the medicine and food
This medicine may be taken with or without food.

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

Pregnancy
There is a risk of harmful effects on the developing baby. Therefore, do not take this medicine during pregnancy, unless it has been specifically prescribed by the doctor.
You should use effective contraception before starting treatment, during treatment and for 6 months following treatment with this medicine. If you become pregnant while taking this medicine or after you have taken it, you should contact your doctor.

Breastfeeding
Do not take Hydroxyurea medac while breastfeeding, unless it has been specifically prescribed by the doctor. The active ingredient of Hydroxyurea medac passes into breastmilk.

Fertility
During the treatment and for three months after stopping the treatment, men are advised to use effective contraception. Ask the doctor regarding the possibility of sperm preservation before starting the first treatment.
Patients who are planning to have children after the treatment are advised to seek genetic counselling.

Driving and operating machinery
The ability to react may be impaired during treatment with Hydroxyurea medac. You should bear this in mind when heightened attention is required, for example, while driving and operating machinery.

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

This medicine contains sodium
This medicine contains less than 1 mmol sodium (23 milligrams) in each capsule, which means it is essentially “sodium-free”.

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 uncertain about the dosage and how to use the medicine.
The dosage and treatment regimen will be determined only by the doctor.

The generally accepted dosage is:
Adults
In chronic myeloid leukemia, the common starting dosage is 40 mg/kg body weight, daily. Afterwards, the dosage is individually adjusted according to the white blood cell count.

In polycythemia vera, the common starting dosage is 15-20 mg/kg body weight, daily. Afterwards, the dosage is individually adjusted to 1-2 capsules (500-1,000 mg) according to the blood cell count.

In essential thrombocythemia, the common starting dosage is 15 mg/kg body weight daily, with individual dosage adjustment according to 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.

How to take the medicine

- Swallow the capsules whole and do not let them break down in the mouth. Do not open the capsule and do not disperse its content.
- Handle the capsules carefully. You should use gloves or wash your hands thoroughly after handling them.
- Even if the risks to the fetus are minimal, pregnant women should avoid handling the capsules.

If you accidentally take a higher dose, you should inform the doctor immediately.
If you accidentally take a higher dosage of this medicine than you have been prescribed, always refer to the doctor or 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 this medicine, refer immediately to a doctor or to a hospital emergency room and take the package of the medicine with you.

If you forget to take this medicine
It is important to follow the treatment exactly as prescribed by the doctor.
Do not take a double dose in order to compensate for a forgotten dose.
If you miss one dose, continue the treatment as prescribed. If you miss several doses, continue the treatment as prescribed, but contact the doctor for further advice.

Follow the treatment as recommended by the doctor.
Even if there is an improvement in your health condition, do not stop treatment with the medicine without consulting the doctor.

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

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

4. Side effects
As with any medicine, using Hydroxyurea medac may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.

Contact your doctor immediately if you experience symptoms such as:
- Fever, cough or breathing problems, this can be a sign of a serious lung disease (unknown frequency)
- High fever (above 39°C) accompanied by problems in the stomach, lungs, muscles, liver, skin and heart, within 6 weeks of taking Hydroxyurea medac (frequency: rare)

Very common side effects (may affect more than 1 out of 10 users):
- Absence or low amount of sperm in the semen (azoospermia or oligospermia)
- Decrease in the number of blood cells (suppression of bone marrow function), especially white blood cells (leukocytopenia), including a type of white blood cell which helps the body to fight the disease (a decrease in CD4 lymphocytes), red blood cells (anemia) and platelets (thrombocytopenia)
- Nausea, vomiting, loss of appetite, mouth sores (stomatitis), diarrhea, constipation, abdominal pain, inflammation of the gastrointestinal mucosa (mucositis), indigestion (dyspepsia)
- Black tarry stool or blood in the stool
- In combination with certain HIV treatments: inflammation of the pancreas (pancreatitis) with pain in the stomach or abdomen
- Drug-induced fever, chills, feeling of discomfort, weakness, loss of energy

- Skin ulcers, especially leg ulcers
- Skin rashes in the form of spots or blisters (maculopapular rash), redness of the face, redness of the hands and feet (hand and foot syndrome)
- Changes in the skin such as a purple rash and thinning of the skin; darkening and atrophy of the nails and skin, purple, small, itchy bumps on the skin; peeling of the skin (scales), blackening and death of the skin
- Hair loss (alopecia)
- Temporary kidney problems with an elevation of certain blood parameters such as uric acid, urea and creatinine
- Difficulty urinating

Common side effects (may affect up to 1 out of 10 users):
- Enlarged, immature red blood cells (megaloblastosis)
- Skin cancer
- Increased liver enzymes
- Inflammation of the liver (hepatitis) causing flu-like symptoms, including tiredness, loss of appetite, fever, pain, and nausea/vomiting, pressure or pain under the right ribs and may also include yellowing of the skin or eyes
- Problems with bile flow (cholestasis). The bile which is produced by the liver to help in the digestion of food may not flow properly. Accumulation of bile can cause itching, yellow skin, very dark urine and very pale stool
- Neurological disorders including headaches, dizziness, drowsiness, disorientation, hallucinations and convulsions
- Acute and chronic lung reactions, with changes in lung tissue seen in x-ray 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 (liver toxicity)

Uncommon side effect (may affect up to 1 out of 100 users):
- Thick and scaly skin patches (actinic keratosis)
- High levels of breakdown products of red blood cells (bilirubin) in the blood

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

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

Side effects with unknown frequency (frequency cannot be estimated from the available data):
- High levels of potassium in the blood, which can cause an abnormal heart rate
- Fever, cough or breathing problems, this can be a sign of a serious lung disease; allergic inflammation of the air sacs
- Hemolytic anemia
- Dry skin

In the post-marketing follow-up, cases of low sodium levels have been observed, which can cause tiredness and confusion, muscle spasms, convulsions or coma.

If you are receiving long-term treatment with hydroxycarbamide, secondary leukemia (blood cancer) may develop. It is currently not known to what extent this results from your underlying disease or from treatment with hydroxycarbamide.

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 your doctor.

Reporting of side effects
Side effects may be reported to the Ministry of Health by clicking on the link "Report side effects due to medicinal treatment" found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or by clicking on the following link: https://sideeffects.health.gov.il

5. How to store the medicine?

- 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 an explicit instruction from the doctor.
- Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.
- Store below 25°C.
- Do not discard medicines in wastewater or a domestic trash can. Ask your pharmacist how to destroy medicines no longer in use. These measures will help to protect the environment.

6. Additional information

In addition to the active ingredient the medicine also contains:
Capsule contents:
Disodium citrate, lactose monohydrate, calcium citrate, magnesium stearate

The capsule shell:
Gelatin, titanium dioxide (E171)

What does the medicine look like and what are the contents of the package?
White gelatin capsules filled with off-white powder.
Available in packages of 100 capsules.

Name and address of the marketing authorization holder:
Tzamal Bio-pharma Ltd., 20 Hamagshimim St., Kiryat Matalon, Petach Tikva.

Name and address of the manufacturer:
Medac Gesellschaft für klinische Spezialpräparate m.b.H., Theaterstrasse 6, 22880, Wedel, Germany.

This leaflet was revised in November 2024.

Registration number of the medicine in the national drug registry of the Ministry of Health: 168-84-35373-00