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

The medicine is dispensed with a doctor's prescription only

RYDAPT® 25 mg Soft capsules

Active ingredient:
Each soft capsule contains:
midostaurin 25 mg

Inactive and allergenic ingredients: see section 2 "Important information about some of the ingredients of the medicine" and section 6 "Further information".

Read this 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?

Acute myeloid leukemia

Rydapt is intended for the treatment of newly diagnosed acute myeloid leukemia (AML) in combination with standard chemotherapy treatment (including induction and consolidation) and then as maintenance monotherapy, in adults who have a defect in the gene called FLT3.

Advanced systemic mastocytosis

Rydapt is intended for treatment of adult patients with a disease called advanced systemic mastocytosis (ASM).

Therapeutic group: Protein kinase inhibitors.

Rydapt contains the active ingredient midostaurin, which belongs to a group of medicines called protein kinase inhibitors. Midostaurin blocks the action of certain enzymes (kinases) in abnormal cells and stops their division and growth.

Acute myeloid leukemia is a type of cancer of certain white blood cells. In acute myeloid leukemia, the body produces too many abnormal blood cells (called "myeloid" cells).

At the start of treatment of acute myeloid leukemia, Rydapt is always given in combination with chemotherapy (medicines for treating cancer).

In a disease called advanced systemic mastocytosis, the body produces too many mast cells, a type of white blood cell. The symptoms are caused when too many mast cells infiltrate organs such as the liver, bone marrow or spleen and release substances such as histamine into the blood.

2. BEFORE USING THE MEDICINE

Follow the doctor's instructions carefully. They may differ from the general information in this leaflet.

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient midostaurin or to any of the additional ingredients contained in the medicine (see section 6 "Further information").
  If you think you may be sensitive, consult the doctor.
- You are already taking one of the following medicines:
  - medicines to treat tuberculosis, such as rifampicin;
  - medicines to treat epilepsy, such as carbamazepine or phenytoin;
  - enzalutamide, a medicine used to treat prostate cancer;
  - St. John's wort (also known as *Hypericum perforatum*), a herbal medicine used to treat depression.

Avoid taking these medicines during treatment with Rydapt. Tell your doctor if you are told that you have to start taking one of these medicines during treatment with Rydapt.

Special warnings regarding use of this medicine

Before beginning treatment with Rydapt, tell a doctor if:
- you have any infections.
- you have impaired heart function.
- you have lung function problems or breathing problems.

Tell a doctor or pharmacist immediately if you have any of the following symptoms during treatment with Rydapt:
- If you have a fever, sore throat or mouth ulcers, because these may be signs that indicate that your white blood cell level is low.
- If you have new or worsening symptoms such as fever, cough with or without phlegm, chest pain, trouble breathing or shortness of breath, because these may be signs of lung function problems.
- If you have chest pain or discomfort, light-headedness, fainting, dizziness, blue discoloration of your lips, hands or feet, shortness of breath or swelling (edema) of your lower limbs or skin, because these may be signs of heart problems.

Your doctor may need to adjust, temporarily stop or completely discontinue your treatment with Rydapt.

Children and adolescents
Rydapt is not indicated for children and adolescents under 18 years of age.

Tests and follow-up
Your doctor will perform regular blood tests during treatment with Rydapt in order to monitor the number of blood cells (white blood cells, red blood cells and platelets) and electrolytes (e.g., calcium, potassium, magnesium) in your body. Your heart and lung function will also be checked regularly.

Drug interactions

If you are taking or have recently taken other medicines including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. This is because Rydapt can affect the way certain medicines work. Other medicines can also affect the way Rydapt works.

Avoid taking the following medicines while being treated with Rydapt:
- medicines to treat tuberculosis, such as rifampicin;
- medicines to treat epilepsy, such as carbamazepine or phenytoin;
- enzalutamide, a medicine to treat prostate cancer;
- St. John's wort (also known as *Hypericum perforatum*), a herbal medicine to treat depression.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- certain medicines used to treat infections, such as ketoconazole or clarithromycin;
- certain medicines used to treat the immunodeficiency virus (HIV), such as ritonavir or efavirenz;
- certain medicines to treat depression, such as nefazodone or bupropion;
- certain medicines to control levels of fats in the blood, such as atorvastatin or rosuvastatin;
- tizanidine, a medicine used to relax muscles;
- chlorzoxazone, a medicine used for treating discomfort caused by muscle spasms.

If you are taking any of these, your doctor may prescribe for you a different medicine during the course of treatment with Rydapt.

Also tell your doctor if you are already taking Rydapt and a new medicine that you have not taken previously has been prescribed for you during treatment with Rydapt.
Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

Use of the medicine and food
Take Rydapt with food.

Pregnancy, breastfeeding and fertility
Rydapt may harm your fetus and therefore, is not recommended during the course of pregnancy.
If you are pregnant, think you may be pregnant, or are planning to become pregnant, consult with your doctor before taking this medicine. Rydapt may harm your baby. Do not breastfeed during treatment with Rydapt and for at least 4 months after completing the treatment.
Rydapt may impair fertility in men and women. Consult your doctor before starting treatment.

Contraceptives in women
If you become pregnant during the course of treatment with Rydapt, it may harm your baby. Your doctor will ask you to perform a pregnancy test before starting treatment with Rydapt to make sure you are not pregnant. You must use an effective method of contraception while taking Rydapt and for at least 4 months after completing the treatment. The doctor will discuss with you the most suitable method of contraception for you to use.

If you become pregnant or think you are pregnant, **tell a doctor immediately**.

Driving and operating machinery
Exercise caution when driving or operating machinery, since you may develop dizziness and light-headedness with loss of balance (vertigo) when taking Rydapt.

Important information about some of the ingredients of the medicine
Rydapt contains ethanol anhydrous (alcohol)
This medicine contains 666 mg of alcohol (ethanol) in each 200 mg dose (maximum daily dose), which is equivalent to 14% (% vol.) ethanol anhydrous. The amount in a 200 mg dose of this medicine is equivalent to 17 ml beer or 7 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects. Alcohol may be harmful if you have alcohol-related problems, epilepsy or liver problems, or if you are pregnant or breastfeeding.
Rydapt contains macrogolglycerol hydroxystearate (castor oil)
This medicine contains the ingredient macrogolglycerol hydroxystearate (castor oil), which may cause abdominal discomfort and diarrhea.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use this medicine according to the doctor's instructions.
Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the medicine.
The dosage and treatment regimen will be determined by the doctor only.
The usual dose is generally:
Patients with acute myeloid leukemia:
50 mg (2 capsules), twice daily (4 capsules per day).
Patients with advanced systemic mastocytosis:
100 mg (4 capsules), twice daily (8 capsules per day).
Depending on your response to Rydapt, your doctor may prescribe a lower dosage for you or temporarily interrupt the treatment.

Do not exceed the recommended dosage.

When to take Rydapt
- Take the capsules at the same time every day. This will help you remember when to take the medicine.
- Take Rydapt twice a day at intervals of approximately 12 hours (e.g., with breakfast and dinner).
- Take Rydapt with food.

How to take Rydapt
- Swallow the capsules whole with a glass of water. Do not open, chew or crush the capsules to ensure administration of the correct dose and avoid the unpleasant taste of the capsule content.
- In patients with acute myeloid leukemia, Rydapt is first given in combination with chemotherapy and then given as a monotherapy. It is very important to follow your doctor's instructions.
- If you have vomited after you swallowed the capsules, do not take another dose of Rydapt. Take the next dose at the regular time.

How long to take Rydapt
- Continue taking Rydapt for as long as the doctor instructs you to do so. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.
- If you are receiving the treatment for acute myeloid leukemia, after the period in which Rydapt is given together with other chemotherapy treatments, you will receive Rydapt alone for a period of up to 12 months.
- If you are receiving treatment for advanced systemic mastocytosis, you will be given Rydapt as a long-term treatment.

If you have questions about how long to take Rydapt, talk to your doctor or pharmacist.

If you accidentally took a higher dosage or if someone 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, because medical care may be necessary.

If you forget to take this medicine at the designated time, do not take a double dose. Skip the forgotten dose and take the next dose at the regular time and consult the doctor.

Adhere to the treatment regimen recommended by the doctor.

If you stop taking the medicine
Stopping treatment with Rydapt may cause worsening of the condition. Do not stop treatment with the medicine without instructions from 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 Rydapt may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Stop taking Rydapt and refer to a doctor immediately if any of the following effects occur since they can be signs of an allergic reaction (hypersensitivity):
- difficulty breathing or swallowing
- dizziness
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps.

Some side effects in patients with AML could be serious

Refer to a doctor, pharmacist or nurse immediately if any of the following effects occur:
- Weakness, spontaneous bleeding or bruising, frequent infections with signs such as fever, chills, sore throat or mouth ulcers (signs of a low level of blood cells).
- Fever, cough with or without mucus, chest pain, trouble breathing or shortness of breath (signs of non-infectious interstitial lung disease or pneumonitis).
- Severe shortness of breath, labored and unusually rapid breathing, dizziness, light-headedness, confusion and extreme tiredness (signs of acute respiratory distress syndrome).
- Infections, fever, low blood pressure, decreased urination, rapid pulse, rapid breathing (signs of sepsis or neutropenic sepsis).

Additional possible side effects in patients with AML
Additional side effects include the effects listed below. If one of them worsens, refer to a doctor or pharmacist.
Most of the side effects are mild to moderate and generally disappear after a few weeks of treatment.

Very common side effects (may affect more than 1 in 10 patients)
- Infection at the catheter site
- Red or purple, flat, pinhead-sized spots under the skin
- Problems falling asleep (insomnia)
- Headache
- Shortness of breath, labored breathing
- Abnormal electrocardiogram (ECG) results which can indicate to your doctor that you have an abnormality of the electrical activity of the heart, known as QT prolongation
- Dizziness, light-headedness (low blood pressure)
- Nosebleeds
- Sore throat
- Mouth sores (stomatitis)
- Nausea, vomiting
- Upper abdominal pain
- Hemorrhoids
- Excessive sweating
- Skin rash with flaking or peeling
- Back pain
- Joint pain (arthralgia)
- Fever
- Thirst, high urine output, dark urine, dry and flushed skin (signs of a high level of sugar in the blood, known as hyperglycemia)
- Muscle weakness, drowsiness, confusion, convulsions, impaired consciousness (signs of a high level of sodium in the blood, known as hypernatremia)
- Muscle weakness, muscle spasms, abnormal heart rhythm (signs of a low level of potassium in the blood, known as hypokalemia)
- Bruising and bleeding (blood clotting defect)
- Abnormal blood test results which can provide information to your doctor about the function of certain organs in your body: High levels of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (indicative of liver function).

Common side effects (may affect up to 1 in 10 patients)
- Upper respiratory tract infection
- Nausea, vomiting, constipation, stomach pain, frequent urination, thirst, muscle weakness and spasm (signs of a high level of calcium in the blood, known as hypercalcemia)
- Fainting
- Involuntary shaking of the body
- Headache, dizziness (high blood pressure)
- Fast heartbeat (sinus tachycardia)
- Fluid collection around the heart, which, if severe, may reduce the heart's ability to pump blood (pericardial effusion)
- Fluid collection in the lungs/chest cavity, which, if severe, may cause breathing difficulties for you (pleural effusion)
- Sore throat and runny nose
- Swelling of the eyelid
- Discomfort in the anus and rectum
- Abdominal pain, nausea, vomiting, constipation (abdominal discomfort)
- Dry skin
- Eye pain, blurred vision, intolerance to light (keratitis)
- Neck pain
- Bone pain
- Pain in the limbs
- Increased weight
- Blood clotted in the catheter
- Abnormal blood test results which can provide information to your doctor about the function of certain organs in your body: high levels of uric acid.

Some side effects in patients with advanced systemic mastocytosis could be serious
Refer to a doctor, pharmacist or nurse immediately if any of the following effects occur:
- Weakness, spontaneous bleeding or bruising, frequent infections with signs such as fever, chills, sore throat or mouth ulcers (signs of a low level of blood cells)
- Fever, cough, difficult or painful breathing, wheezing, chest pain when breathing (signs of pneumonia)
- Fever, cough with or without mucus, chest pain, trouble breathing or shortness of breath (signs of non-infectious interstitial lung disease or pneumonitis)
- Infections, fever, dizziness, light-headedness, decreased urination, rapid pulse, rapid breathing (signs of sepsis or neutropenic sepsis)
- Vomiting of blood, black or bloody stools (signs of gastrointestinal bleeding).

Other possible side effects in patients with advanced systemic mastocytosis
Other side effects include those listed below.
If one of them worsens, refer to a doctor or pharmacist.
Most of the side effects are mild to moderate and generally disappear after a few weeks of treatment.

Very common side effects (may affect more than 1 in 10 patients)
- Urinary tract infection
- Upper respiratory tract infection
- Headache
- Dizziness
- Shortness of breath, labored breathing
- Cough
- Fluid collection in the lungs/chest cavity, which, if severe, may cause breathing difficulties for you (pleural effusion)
- Abnormal electrocardiogram (ECG) results which can indicate to your doctor that you have an abnormality of the electrical activity of the heart, known as QT prolongation
- Nosebleeds
- Nausea, vomiting
- Diarrhea
- Constipation
- Rapid weight gain, swelling of the limbs (calves, ankles)
- Feeling very tired (fatigue)
- Fever
- Thirst, high urine output, dark urine, dry flushed skin (signs of a high level of sugar in the blood, known as hyperglycemia)
- Yellow skin and eyes (sign of high bilirubin in the blood)
- Abnormal blood test results which can provide a doctor with information about possible problems with the pancreas (high levels of lipase or amylase) and liver (high levels of alanine aminotransferase [ALT] or aspartate aminotransferase [AST]).

Common side effects (may affect up to 1 in 10 patients)
- Involuntary shaking of the body
- Cough with phlegm, chest pain, fever (bronchitis)
- Cold sores in the mouth due to viral infection (oral herpes)
- Painful and frequent urination (cystitis)
- Feeling of pressure or pain in the cheeks and forehead (sinusitis)
- Red, swollen painful rash on any part of the skin (erysipelas)
- Shingles (herpes zoster)
- Disturbance in the ability to concentrate
- Feeling dizzy with a spinning sensation/loss of balance (vertigo)
- Bruising (hematoma)
- Upset stomach, indigestion
- Feeling weak
- Chills
- Generalized swelling (edema)
- Increased weight
- Contusions (bruises)
- Falls
- Dizziness, light-headedness (low blood pressure)
- Sore throat.

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 with the doctor.

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/

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine should be kept in a safe place out of 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 package and blister. The expiry date refers to the last day of that month.
- **Storage conditions:** Do not store above 30°C. Store in the original package to protect from moisture.
- Do not use the medicine if you notice any damage to the package or signs of tampering.
- Do not dispose of medicines in the wastewater or household waste bin. Ask the pharmacist how to dispose of medicines no longer in use. These measures will help protect the environment.

6. FURTHER INFORMATION

- In addition to the active ingredient, the medicine also contains:

Macrogolglycerol hydroxystearate, gelatin, macrogol 400, glycerol 85%, ethanol anhydrous, corn oil mono-di-triglycerides, titanium dioxide (E171), all-rac-α-tocopherol, iron oxide yellow (E172), iron oxide red (E172), carmine (E120), hypromellose 2910, propylene glycol, purified water.

Each capsule contains approximately 83.30 mg alcohol (ethanol anhydrous).
Each capsule contains 414.83 mg castor oil (macrogolglycerol hydroxystearate).

- What the medicine looks like and the content of the package:
  Rydapt 25 mg capsules are soft, oblong, pale orange capsules with "PKC NVR" imprinted in red.
  The capsules are packaged in blisters; each package contains 56 (2 packs of 28 capsules) or 112 capsules (4 packs of 28 capsules).
  Not all pack sizes may be marketed.
- Registration Holder and Importer and its address: Novartis Israel Ltd., P.O.B 7126, Tel Aviv.
- Revised in April 2022 according to MOH guidelines.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health: 160-65-35320