Package leaflet: Information for the patient

Rydapt® 25 mg soft capsules
midostaurin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rydapt is and what it is used for

What Rydapt is
Rydapt contains the active substance midostaurin. It belongs to a class of medicines called protein kinase inhibitors.

What Rydapt is used for
Rydapt is used to treat acute myeloid leukaemia (AML) in adults who have a defect in a gene called FLT3. Acute myeloid leukaemia is a form of cancer of certain white blood cells (called myeloid cells) in which the body over-produces an abnormal type of these cells.

Rydapt is also used in adults to treat aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL). These are disorders in which the body produces too many mast cells, a type of white blood cell. Symptoms are caused when too many mast cells enter organs such as the liver, bone marrow or spleen, and release substances such as histamine into the blood.

How Rydapt works
Midostaurin blocks the action of some enzymes (kinases) in the abnormal cells and stops their division and growth.

At the start of treatment in AML Rydapt is always used together with chemotherapy (medicines for treating cancer).

If you have any questions about how Rydapt works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take Rydapt

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

Do not take Rydapt
- if you are allergic to midostaurin or to any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- if you are already taking any of the following medicines:
  - medicines used to treat tuberculosis, such as rifampicin;
  - medicines used 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.

  These medicines must be avoided during treatment with Rydapt. Talk to your doctor if you are told that you have to start taking one of them during Rydapt treatment.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Rydapt:
- if you have any infections.
- if you have a heart disorder.
- if you have problems with your lungs or problems breathing.
- if you have problems with your kidneys.

Tell your doctor, pharmacist or nurse straight away if you get any of these symptoms during treatment with Rydapt:
- if you have fever, sore throat or mouth ulcers, because these may indicate that your white blood cell count is low.
- if you have new or worsening symptoms such as fever, cough with or without mucous, chest pain, trouble breathing or shortness of breath, because these may be signs of lung problems.
- if you have or experience chest pain or discomfort, light-headedness, fainting, dizziness, blue discolouration of your lips, hands or feet, shortness of breath, or swelling of your lower limbs (oedema) 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.

<u>Monitoring during treatment with Rydapt</u>
Your doctor will perform regular blood tests during treatment with Rydapt in order to monitor the amount 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.

Children and adolescents
Rydapt should not be used in children and adolescents below 18 years of age who are also receiving other chemotherapy, because it could cause a severe reduction of certain types of blood cells.

Other medicines and Rydapt
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Rydapt can affect the way some medicines work. Some other medicines can also affect how Rydapt works.

The following medicines must be avoided during treatment with Rydapt:
- medicines used to treat tuberculosis, such as rifampicin;
- medicines used 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.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- some medicines used to treat infections, such as ketoconazole or clarithromycin;
- some medicines used to treat HIV, such as ritonavir or efavirenz;
- some medicines used to treat depression, such as nefazodone or bupropion;
- some medicines used to control levels of fat in your 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 medicines, your doctor might prescribe a different medicine for you during your treatment with Rydapt.

You should also tell your doctor if you are already taking Rydapt and you are prescribed a new medicine that you have not previously taken during treatment with Rydapt.

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

Pregnancy and breast-feeding
Rydapt may harm your unborn baby and is not recommended during pregnancy. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Rydapt could harm your baby. You should not breast-feed during treatment with Rydapt and for at least 4 months after stopping the treatment.

Contraception in women
If you become pregnant while taking Rydapt, it may harm your baby. Your doctor will ask you to take a pregnancy test before you start 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 you have stopped taking it. Your 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 your doctor right away.

Fertility
Rydapt may reduce fertility in men and women. You should discuss this with your doctor before starting treatment.

Driving and using machines
Take special care when driving and using machines as you may develop dizziness and vertigo while you are taking Rydapt.

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 breast-feeding.

Rydapt contains macrogolglycerol hydroxystearate (castor oil)
This medicine contains macrogolglycerol hydroxystearate, which may cause stomach discomfort and diarrhoea.

3. How to take Rydapt

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor

or pharmacist if you are not sure.

Do not exceed the dose prescribed by your doctor.

How much Rydapt to take
Your doctor will tell you exactly how many capsules to take.
- *Patients with AML*
  The usual daily dose is 50 mg (2 capsules) twice daily.
- *Patients with ASM, SM-AHN or MCL*
  The usual daily dose is 100 mg (4 capsules) twice daily.

Depending on how you respond to Rydapt, your doctor may lower your dose or temporarily interrupt the treatment.

Taking this medicine
- Taking Rydapt at the same time each day will help you to remember to take your medicine.
- Take Rydapt twice a day at about 12-hour intervals (for example, with breakfast and with your evening meal).
- Take Rydapt with food.
- Swallow the capsules whole with a glass of water. Do not open, crush or chew them to ensure proper dosing and avoid the unpleasant taste of the capsule content.
- For patients with AML, Rydapt is taken with chemotherapy medicines. It is very important to follow your doctor's recommendations.
- If you vomit after you swallow the capsules, do not take any more capsules until your next scheduled dose.

How long to take Rydapt
- Continue taking Rydapt for as long as your doctor tells you. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.
- If you are being treated for AML, after you finish taking Rydapt with chemotherapy medicines, you will receive Rydapt alone for up to 12 months.
- If you are being treated for ASM, SM-AHN or MCL, you will receive Rydapt as a long-term treatment, possibly lasting for months or years.

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

If you take more Rydapt than you should
If you take more capsules than you should, or if someone else takes your medicine, talk to a doctor or go to a hospital straight away, taking the pack with you, as medical treatment may be necessary.

If you forget to take Rydapt
If you forget to take Rydapt, skip the missed dose and take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose. Instead, wait until it is time for your next dose.

If you stop taking Rydapt
Stopping your treatment with Rydapt may cause your condition to become worse. Do not stop taking your medicine unless your doctor tells you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Rydapt and tell your doctor straight away if you notice any of the following as these could be signs of an allergic reaction:
- 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.
Tell your doctor, pharmacist or nurse straight away if you notice any of the following:
- 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, laboured 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)

Other possible side effects in patients with AML
Other side effects include those listed below. If any of these side effects become severe, tell your doctor or pharmacist.

Most of the side effects are mild to moderate and will generally disappear after a few weeks of treatment.

Very common (may affect more than 1 in 10 people)
- infection at catheter site
- red or purple, flat, pinhead spots under the skin (petechiae)
- problems falling asleep (insomnia)
- headache
- shortness of breath, laboured breathing (dyspnoea)
- abnormal electrocardiogram results which can indicate to your doctor that you have an abnormality of the electrical activity of your heart known as QT prolongation
- dizziness, light-headedness (low blood pressure)
- nose bleeds
- throat pain (laryngeal pain)
- mouth sores (stomatitis)
- nausea, vomiting
- upper abdominal pain
- haemorrhoids (piles)
- excessive sweating
- skin rash with flaking or peeling (exfoliative dermatitis)
- back pain
- joint pain (arthralgia)
- fever
- thirst, high urine output, dark urine, dry flushed skin (signs of high levels of sugar in the blood, known as hyperglycaemia)
- muscle weakness, drowsiness, confusion, convulsions, impaired consciousness (signs of high level of sodium in the blood, known as hypernatraemia)
- muscle weakness, muscle spasms, abnormal heart rhythm (signs of low levels of potassium in the blood, known as hypokalaemia)
- bruising and bleeding (defect in blood clotting)
- abnormal blood test results which can indicate to your doctor how well certain parts of your body are functioning: high levels of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (indicative of liver function)

Common (may affect up to 1 in every 10 people)
- upper respiratory tract infection
- nausea, vomiting, constipation, stomach pain, frequent urination, thirst, muscle weakness and twitching (signs of high levels of calcium in the blood, known as hypercalcaemia)

- fainting
- involuntary shaking of the body
- headache, dizziness (high blood pressure)
- fast heart beat (sinus tachycardia)
- collection of fluid around the heart, which, if severe, can decrease the heart's ability to pump blood (pericardial effusion)
- fluid collection in the lungs/chest cavity, which, if severe, could make you breathless (pleural effusion)
- sore throat and a 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 limbs
- increased weight
- blood clotted in the catheter
- abnormal blood test results which can indicate to your doctor how well certain parts of your body are functioning: high levels of uric acid

Not known (frequency cannot be estimated from the available data)
- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)

Some side effects in patients with ASM, SM-AHN and MCL could be serious.
Tell your doctor, pharmacist or nurse straight away if you notice any of the following:
- 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 in 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 ASM, SM-AHN and MCL
Other side effects include those listed below. If any of these side effects become severe, tell your doctor or pharmacist.

Most of the side effects are mild to moderate and will generally disappear after a few weeks of treatment.

Very common (may affect more than 1 in 10 people)
- urinary tract infection
- upper respiratory tract infection
- headache
- dizziness
- shortness of breath, laboured breathing (dyspnoea)
- cough
- fluid collection in the lungs/chest cavity, which, if severe, could make you breathless (pleural effusion)
- abnormal electrocardiogram results which can indicate to your doctor that you have an abnormality of the electrical activity of your heart known as QT prolongation
- nose bleeds

- nausea, vomiting
- diarrhoea
- constipation
- swelling of the limbs (calves, ankles)
- feeling very tired (fatigue)
- fever
- thirst, high urine output, dark urine, dry flushed skin (signs of high levels of sugar in the blood, known as hyperglycaemia)
- yellow skin and eyes (sign of high bilirubin in the blood)
- abnormal blood test results which indicate possible problems with the pancreas (high levels of lipase or amylase) and liver (high levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST))

Common (may affect up to 1 in every 10 people)
- 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 attention
- feeling dizzy with spinning sensation (vertigo)
- bruising (haematoma)
- upset stomach, indigestion
- feeling weak (asthenia)
- chills
- generalised swelling (oedema)
- increased weight
- contusion (bruises)
- falls
- dizziness, light-headedness (low blood pressure)
- sore throat
- rapid weight gain

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rydapt

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and the blister foil after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special temperature storage conditions. Store in the original container in order to protect from moisture.
- Do not use this medicine if you notice any damage to the packaging or if there are any signs of tampering.
- 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. Contents of the pack and other information

What Rydapt contains
- The active substance is midostaurin. Each soft capsule contains 25 mg midostaurin.
- The other ingredients are: macrogolglycerol hydroxystearate (see "Rydapt contains macrogolglycerol hydroxystearate (castor oil)" in section 2), gelatin, macrogol, glycerol, ethanol anhydrous (see "Rydapt contains ethanol anhydrous (alcohol)" in section 2), maize oil mono-di-triglycerides, titanium dioxide (E171), all-rac-alpha-tocopherol, iron oxide yellow (E172), iron oxide red (E172), carmine (E120), hypromellose, propylene glycol, purified water.

What Rydapt looks like and contents of the pack
Rydapt 25 mg soft capsules (capsules) are pale orange, oblong capsules with red imprint "PKC NVR".

The capsules are provided in blisters and are available in packs containing 56 capsules (2 packs of 28 capsules) or 112 capsules (4 packs of 28 capsules). Not all pack sizes may be marketed in your country.

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This leaflet was last revised in 12/2024