

**Patient package insert according to Pharmacists' Regulations (Preparations) – 1986**

This medicine can be sold with a physician's prescription only

## **Ryeqo**

### **Film-coated tablets**

Each film-coated tablet contains:

Relugolix 40 mg

Estradiol (as hemihydrate) 1 mg

Norethisterone acetate 0.5 mg

Inactive ingredients and allergens in the medicine – see section 6 "Additional information" and in section 2 "Important information about some of the ingredients of the medicine".

**Read this entire leaflet carefully before using the medicine.** This leaflet contains concise information about the medicine. If you have any further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if you think that their medical condition is similar to yours.

#### **1. What is the medicine intended for?**

**Ryeqo** is intended for adult women of childbearing age:

- For treatment of moderate to severe symptoms of uterine fibroids.
- For treatment of symptoms associated with endometriosis in women with a history of previous medical or surgical treatment of endometriosis.

**Therapeutic group:** hormones and analogues of the pituitary gland and hypothalamus, gonadotropin-releasing hormone inhibitor.

Uterine fibroids (also known as myomas), are non-cancerous tumors in the uterus. In some women, uterine fibroids may cause heavy menstrual bleeding (your "period") and pelvic pain (pain below the belly button). **Ryeqo** is used for the treatment of your fibroids in order to stop or reduce bleeding and to decrease pelvic pain and discomfort associated with uterine fibroids.

Endometriosis is a usually painful disease, in which tissue similar to the tissue that normally lines the inside of the uterus (endometrium) grows outside the uterus. Women with endometriosis may experience pelvic or lower abdominal pain, pain during menstruation and pain during sexual intercourse. **Ryeqo** is used for the treatment of endometriosis to decrease the symptoms caused due to the growth of the tissue outside the endometrium.

This medicine contains relugolix, which blocks certain receptors in the brain and thus reduces the production of the hormones that stimulate the ovaries to produce estradiol and progesterone. When the receptors are blocked, the levels of estrogen and progesterone in the body are reduced. This medicine also contains two types of female hormones: estradiol, which belongs to a group of medicines called estrogens, and norethisterone, which belongs to a group of medicines called progestogens. The inclusion of these hormones in **Ryeqo** maintains a hormonal state similar to the beginning of your menstrual cycle and thus relieves your symptoms while helping to protect the strength of your bones.

#### **2. Before using the medicine**

Do not take **Ryeqo** if you have any of the conditions listed below.

If you have any of the conditions listed below, you must tell the doctor.

**Do not use the medicine if:**

- You are **hypersensitive (allergic)** to the active ingredients (relugolix, estradiol, norethisterone acetate) or to any of the other ingredients this medicine contains (see section 6).
- You have or have previously had a **blood clot in a blood vessel** in the legs (deep vein thrombosis), lungs (pulmonary embolism), heart (heart attack), brain (stroke) or any other part of the body.
- You have or have previously had a disease caused by blood clots in the arteries, such as **heart attack, stroke or angina pectoris**.
- You have a **blood clotting disorder** (such as protein C deficiency, protein S deficiency, antithrombin III deficiency or factor V Leiden).
- You have **osteoporosis**.
- You suffer from **headaches** with focal neurological symptoms such as paralysis or loss of muscle control, or **migraines** with visual disturbance.
- You have any type of **cancer** or suspected cancer that may worsen by exposure to female sex hormones, such as **cancer of the breast or genitals**.
- You have or have previously had **tumors in the liver**.
- You have or have previously had a **liver disease and your liver function tests** have not returned to normal.
- You are **pregnant** or think you **may be pregnant** or if you are **breastfeeding**.
- You have **genital bleeding** of unknown origin.
- You are taking **hormonal contraceptives** (such as contraceptive pills).

If any of the above conditions appear for the first time while taking **Ryeqo**, stop taking it immediately and consult your doctor immediately.

If you are not sure about any of the points above, talk to your doctor before taking **Ryeqo**.

**Special warnings regarding the use of the medicine**

Talk to your doctor or pharmacist before taking **Ryeqo**.

You should know that most women experience reduced or lack of menstrual bleeding during treatment and for a few weeks afterwards.

Your doctor will discuss your medical and family history with you. Your doctor will also need to check your blood pressure and ensure you are not pregnant. You may also need to undergo a physical examination and additional tests, such as breast examination and a scan to measure the strength of your bones, according to your medical needs and/or concerns.

**Stop taking Ryeqo and seek urgent medical attention if any of the following appear:**

- Any of the conditions mentioned in the section "Do not use the medicine if".
- If you notice signs of **liver disease**:
  - Yellowing of the skin or of the white of the eyes (jaundice).
  - Nausea or vomiting, fever, severe tiredness.
  - Dark urine, itching or upper abdominal pain.
- A large increase in your **blood pressure** (the symptoms may be headache, fatigue, dizziness).
- **Migraine** for the first time or particularly severe **headaches** occurring more often than in the past.
- If you notice possible signs of a **blood clot**, this means that you may be suffering from a clot in the leg (deep vein thrombosis) or in the lung (pulmonary embolism), heart attack or stroke. For a description of the symptoms of these serious conditions, see in section "**Ryeqo** and the risk of blood clots".
- If you become **pregnant**.

**Tell your doctor if any of the following conditions apply to you:**

- You have one or more of the **risk factors for developing a blood clot** listed below.
- You have **high blood pressure**.
- You have **osteoporosis**.
- You suffer from **migraines**.
- You think you might be **pregnant**. Treatment with **Ryeqo** usually leads to a significant reduction or may even stop your menstrual bleeding (your “period”), making it difficult to recognize pregnancy.
- You suffer or have previously suffered from **depression**.
- You have **kidney disease**.

**Ryeqo and the risk of blood clots**

The use of other medicines containing estrogen and progestogen increases the risk of blood clots. The risk of blood clots with **Ryeqo** has not been established. **Ryeqo** reduces the estrogen to levels similar to those at the beginning of your normal menstrual cycle.

Factors that can increase your risk of a blood clot in a vein and/or artery:

- With **the increase of age** (particularly above the age of 35).
- If you are overweight (body mass index [BMI] above **30 kg/meter<sup>2</sup>**).
- If you have had **major surgery** or **prolonged time without movement** (e.g., your leg is in a cast).
- If you have **recently given birth**.
- If someone in your close family has had a **blood clot in the leg, lung or another organ, heart attack** or **stroke at a young age** (e.g., below the age of 50).
- If you **smoke**.
- If you have a heart problem (**valve disorder**, disturbance of the rhythm called **atrial fibrillation**).
- If you have **diabetes**.
- If you have certain medical conditions such as **systemic lupus erythematosus** (SLE – a disease that affects the immune system), **sickle cell anemia** (an inherited disease of the red blood cells), **Crohn’s disease** or **ulcerative colitis** (chronic inflammatory bowel diseases) or **cancer**.

The risk of developing a blood clot increases the more risk factors you have.

The symptoms of a blood clot depend on where the clot has appeared.

**Symptoms of a blood clot in the leg (deep vein thrombosis; DVT)**

The symptoms of a blood clot in the leg, known as deep vein thrombosis (DVT), can include:

- Swelling of the leg and/or foot or along a vein in the leg.
- Pain or tenderness in the leg that worsens when switching to a standing position or while walking.
- Increased heat in the affected leg with red skin or skin discoloration.

**Symptoms of a blood clot in the lung (pulmonary embolism; PE)**

The symptoms of a blood clot in the lung, known as pulmonary embolism (PE), can include:

- A sudden onset of unexplained shortness of breath or rapid breathing.
- Sudden coughing which can be accompanied by a sharp pain in the chest.
- Coughing up blood.
- Severe dizziness or feeling lightheaded.
- Fast or irregular heartbeat.

**Symptoms of a heart attack**

The symptoms of a heart attack, also known as a myocardial infarction, may be temporary and can include:

- Pain, discomfort, pressure, heaviness, sensation of pressure or fullness in the chest, arm or below the breastbone.
- Discomfort that radiates to the back, jaw, throat, arm, stomach.
- Sensation of fullness, indigestion or choking.
- Sweating, nausea, vomiting or dizziness.
- Extreme weakness, anxiety or shortness of breath.
- Fast or irregular heartbeat.

### **Symptoms of a stroke**

Symptoms of a stroke can include:

- Sudden onset of numbness or weakness in the face, arm or leg, especially on one side of the body.
- Sudden onset of walking problems, dizziness, loss of balance or coordination.
- Sudden onset of confusion, speech problems or problems understanding others.
- Sudden vision problem in one or both eyes.
- Sudden, severe or prolonged headache with no known cause.
- Loss of consciousness or fainting with or without a convulsion.

### **Surgery**

If you are about to undergo surgery, tell the surgeon that you are taking **Ryeqo**.

### **Liver tumors or liver disease**

In rare cases, liver tumors or liver disease have been reported in women taking estrogens and progestogens. If you experience symptoms of jaundice, refer to your doctor for further medical consultation.

### **Impaired kidney function**

If you experience any decrease in urine production or if you notice any fluid retention causing swelling in the legs, ankles or feet, refer to your doctor for further medical consultation.

### **Change in menstrual bleeding pattern (your “period”)**

Treatment with **Ryeqo** usually leads to a significant reduction or may even stop your menstrual bleeding (your “period”) during the first 30 days of treatment. However, if you continue to experience excessive bleeding, tell your doctor.

### **Depression**

If you experience mood changes or any depressive symptoms, refer to your doctor for further medical consultation.

### **Rise in blood pressure**

In rare cases, treatment with **Ryeqo** may lead to small increases in blood pressure. If you experience any symptoms of increased blood pressure, refer to your doctor for further medical consultation.

### **Uterine fibroid prolapse and expulsion**

Uterine fibroids can develop anywhere in the muscular wall of the uterus, including the submucosa, a thin layer of tissue inside the uterus. In some women, the uterine fibroid may protrude or slip through the cervix into the vagina and may cause significant worsening of uterine bleeding or pain. If you experience severe uterine bleeding again after your symptoms have improved during treatment with **Ryeqo**, refer to your doctor for medical consultation.

### **Gallbladder disorders**

Some women taking estrogen and progestogen hormones, including **Ryeqo**, have reported gallbladder disorders (gallstones or inflammation of the gallbladder). If you experience

unusually severe pain below the rib cage or in the upper abdomen, refer to your doctor for medical consultation.

### Girls and female adolescents

**Ryeqo** is intended for administration to women aged 18 years and above. Do not give this medicine to girls and female adolescents under the age of 18, since the safety and efficacy of **Ryeqo** have not been tested in this age group.

### Drug interactions

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

Tell the doctor if you are taking any of the medicines listed below, as these medicines can affect **Ryeqo** or be affected by **Ryeqo**:

- **Hormonal contraceptives:** see section 2: "Do not use the medicine if".
- Certain medicines used for treatment of **epilepsy** (for example carbamazepine, topiramate, phenytoin, phenobarbital, primidone, oxcarbazepine, felbamate).
- Certain medicines used for treatment of AIDS virus infection/acquired immunodeficiency syndrome (**HIV/AIDS**) (for example ritonavir, efavirenz).
- Certain medicines used for treatment of **hepatitis C virus (HCV)** (for example boceprevir, sofosbuvir, velpatasvir, voxilaprevir, telaprevir, glecaprevir).
- Certain medicines used for treatment of **fungal infections** (for example ketoconazole, itraconazole, fluconazole, griseofulvin).
- Certain medicines used for treatment of **bacterial infections** (for example rifampicin, rifabutin, clarithromycin, erythromycin, gentamicin, tetracycline, griseofulvin).
- A certain medicine used for treatment of **high blood pressure in the arteries of the lung** (for example bosentan).
- Certain medicines used for treatment of **high blood pressure** (for example diltiazem, carvedilol, verapamil).
- Certain medicines used for treatment of **irregular heartbeat** (for example amiodarone, dronedarone, propafenone, quinidine, verapamil).
- Certain medicines used for treatment of **angina pectoris** (for example ranolazine, carvedilol, verapamil).
- Certain medicines for prevention of organ rejection **after transplantation** (for example cyclosporine).
- Herbal medicines containing **St John's wort** (*Hypericum perforatum*).

### Use of the medicine and food

The tablet should be taken orally every day, at about the same time, with or without food and with some water.

### Pregnancy and breastfeeding

Do not take **Ryeqo** if you are pregnant or breastfeeding (see section 2: "Do not use the medicine if").

The doctor will consider the increased risk of vein thrombosis during the postpartum period, when restarting treatment with **Ryeqo**.

### Pregnancy

If you think you may be pregnant or are planning to become pregnant, consult the doctor before taking this medicine. If you become pregnant, stop taking **Ryeqo** and refer to your doctor.

### Breastfeeding

No information is available regarding the presence of relugolix or its metabolites (breakdown substances) in breast milk, or regarding their effect on the breastfed baby. Low amounts of

estrogen and progestogens were identified in the breast milk of women treated with estrogen and progestogen. An effect on newborns/breastfed babies cannot be excluded.

### **Fertility**

**Ryeqo** stops ovulation and often causes lack of menstruation, and therefore it is unlikely that you will become pregnant while using **Ryeqo** if taken as recommended. The ovulation and menstrual bleeding will return rapidly after discontinuing **Ryeqo**. To prevent pregnancy, you should start using an alternative contraceptive immediately after discontinuing **Ryeqo**.

Depending on when in your cycle you start taking **Ryeqo**, it may take time until full inhibition of ovulation by **Ryeqo**; therefore, a nonhormonal contraceptive (e.g., condoms) should be used during the first month after starting the use of **Ryeqo**.

If you miss two tablets or more in a row, a nonhormonal contraceptive (e.g., condoms) should be used for the next 7 days of treatment.

### **Driving and using machines**

**Ryeqo** has no effect or negligible effect on the ability to drive and operate machinery.

### **Laboratory tests**

If you need to have a blood or urine test, tell your doctor or the laboratory staff that you are taking **Ryeqo**, as this medicine can affect the results of certain tests.

### **Important information about some of the ingredients of the medicine**

**Ryeqo** contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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

## **3. How to use the medicine?**

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about the dosage and the manner of treatment with the medicine. The dosage and manner of treatment will be determined by the doctor only.

The generally accepted dosage is one tablet per day.

**Do not exceed the recommended dose.**

### **Method of administration**

The tablet should be taken orally every day, at about the same time, with or without food, with some water.

Do not halve the tablet, as there is no score line. No information is available regarding crushing/chewing.

It is recommended to start taking **Ryeqo** during the first 5 days after the start of your menstrual bleeding. If you start at a different time of the menstrual cycle, you may initially experience irregular or heavier bleeding.

### **If you have accidentally taken a higher dosage**

There have been no reports of serious side effects due to taking several doses of this medicine at once. Large doses of estrogen may cause nausea, vomiting and vaginal bleeding. If you have taken too many **Ryeqo** tablets, consult the doctor or pharmacist.

If a child swallows this medicine by mistake, immediately go to the doctor or to a hospital emergency room and bring the package of the medicine with you.

**If you forgot to take the medicine**

If you miss one tablet, take it as soon as you remember and then continue taking the tablet the next day as usual.

Do not take a double dose in order to compensate for the forgotten dose.

If you miss two tablets or more in a row, consult your doctor and use a nonhormonal contraceptive (e.g., condoms) during the next 7 days of treatment.

**If you stop taking the medicine**

If you would like to stop taking **Ryeqo**, talk to your doctor first. Your doctor will explain the effects of discontinuing treatment and discuss other possibilities with you.

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

**If you have further questions on the use of this medicine, consult the doctor or pharmacist.**

**4. Side effects**

Like any medicine, the use of **Ryeqo** 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.

Seek urgent medical assistance if you experience any of the following signs and symptoms of an allergic reaction:

- Swelling of the lips, face or throat.

The following side effects have been reported with the use of **Ryeqo** and are listed below according to the frequency in which they occur.

**Very common side effects** (effects that occur in more than one user out of ten):

- Headache
- Hot flashes

**Common side effects** (effects that occur in 1-10 users out of 100):

- Irritability
- Decreased libido
- Dizziness
- Nausea
- Hair loss
- Increased sweating
- Night sweats
- Joint pain
- Excessive, irregular or prolonged bleeding from the uterus (uterine bleeding)
- Dryness of the genital area

**Uncommon side effects** (effects that occur in 1-10 users out of 1,000):

- Indigestion
- Hives (urticaria)
- Angioedema (rapid swelling of the mucous membranes or the skin, which may occur in the face, mouth, tongue, abdomen or arms and legs)
- A lump in the breast tissue (breast cyst)
- Uterine myoma expulsion (the fibroid comes out completely or partially through the vagina, usually with increased bleeding from the vagina)

**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.**

Side effects can be reported to the Ministry of Health by clicking the link "דיווח על תופעות לוואי עקב טיפול תרופתי" found on the homepage of the Ministry of Health website ([www.health.gov.il](http://www.health.gov.il)) directing to the online form for reporting side effects or via the link: <https://sideeffects.health.gov.il>

## **5. How to store the medicine?**

- Avoid poisoning! This medicine and any other medicine must be stored in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use this medicine after the expiry date (Expiry date) stated on the package. The expiry date refers to the last day of that month.
- **Storage conditions:** this medicine does not require any special storage conditions. It is recommended to store at room temperature.
- Do not throw away any medicines via wastewater or household waste. Ask the pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Additional information**

**In addition to the active ingredients, the medicine also contains:**

Lactose monohydrate, mannitol, sodium starch glycolate, hydroxypropylcellulose, hypromellose 2910, titanium dioxide (E171), magnesium stearate, triacetin, iron oxide yellow (E172)

**What the medicine looks like and what the package contains:**

A yellow to light yellow, round, film-coated tablet, debossed with "415" on one side and plain on the other side.

Approved package sizes:

Blister package: 14 tablets in a blister packed in a sachet with a desiccant. Each pack contains 28 or 84 tablets.

Bottle package: 28 tablets in a bottle with a desiccant. Each package contains 28 tablets in one bottle or 84 tablets (3 bottles containing 28 tablets each).

Do not swallow the desiccant.

Not all package sizes may be marketed.

**Name and address of the manufacturer:** Gedeon Richter Plc., Budapest, Hungary

This leaflet was checked and approved by the Ministry of Health in July 2025.

**Drug registration number at the national drug registry of the Ministry of Health:**

179-33-38165-99

**Registration holder:** Dexcel Ltd., 1 Dexcel St., Or Akiva 3060000, Israel