ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ryeqo 40 mg/1 mg/0.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg relugolix, 1 mg estradiol (as hemihydrate), and 0.5 mg norethisterone acetate.

Excipient with known effect

Each film-coated tablet contains approximately 80 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Light yellow to yellow, round film-coated tablet of 8 mm with “415” on one side and plain-faced on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ryeqo is indicated in adult women of reproductive age for:
- treatment of moderate to severe symptoms of uterine fibroids,
- symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis (see section 5.1).

4.2 Posology and method of administration

Ryeqo treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of uterine fibroids and/or endometriosis, after careful diagnosis.

Pregnancy must be ruled out prior to initiating treatment.

Posology

The recommended dose is one tablet taken once daily.

When starting treatment, the first tablet must be taken within 5 days of the onset of menstrual bleeding. If treatment is initiated on another day of the menstrual cycle, irregular and/or heavy bleeding may initially occur (see section 4.8).

Ryeqo can be taken without interruption. Discontinuation should be considered when the patient enters menopause, as the symptoms of both uterine fibroids and endometriosis are known to regress when menopause begins.

Bone mineral density (BMD) loss and osteoporosis
A dual X ray absorptiometry (DXA) scan is recommended after 1 year of treatment. In patients with risk factors for osteoporosis or bone loss, a DXA scan is recommended prior to starting Ryeqo treatment (see section 4.4).

Contraceptive properties
Any hormonal contraception needs to be stopped prior to initiation of treatment, as concomitant use of hormonal contraceptives is contraindicated (see section 4.3).

Nonhormonal methods of contraception must be used for at least 1 month after initiation treatment (see section 4.4).

After at least 1 month of treatment, ovulation in women taking the recommended dose is inhibited and provides adequate contraception.

Women of childbearing potential must be advised that ovulation will return rapidly after discontinuing treatment. Therefore, a discussion with the patient, regarding appropriate contraceptive methods, must therefore take place prior to discontinuing treatment and alternative contraception needs to be started immediately after discontinuation of treatment (see section 4.4).

Missed doses
If a dose is missed, the missed tablet must be taken as soon as possible and treatment should be continued with the next tablet at the usual time on the following day.

If two or more tablets are missed for consecutive days, contraceptive protection may be reduced. A nonhormonal method of contraception is to be used for the next 7 days of treatment (see section 4.6).

Elderly
There is no relevant use of this medicinal product in the elderly population (≥65 years).

Renal impairment
No dose adjustment is required in patients with mild, moderate, or severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment is required (see section 5.2). This medicinal product is contraindicated in women with severe liver disease if liver function values have not returned to normal (see section 4.3).

Paediatric population
There is no relevant use of Ryeqo in children aged under 18 years for the treatment of symptoms of uterine fibroids.
The safety and efficacy of Ryeqo in children aged under 18 years for the treatment of endometriosis has not been established. No data are available.

Method of administration

Oral use.

Ryeqo can be taken with or without food, at about the same time. The tablets should be taken with some liquid as needed (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Venous thromboembolic disorder, past or present (e.g. deep venous thrombosis, pulmonary embolism) (see section 4.4).
- Arterial thromboembolic cardiovascular disease, past or present (e.g. myocardial infarction, cerebrovascular accident, ischemic heart disease) (see section 4.4).
- Known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency or activated protein C (APC)-resistance, including Factor V Leiden (see section 4.4).

- Known osteoporosis (see section 4.4).
- Headaches with focal neurological symptoms or migraine headaches with aura (see section 4.4).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Presence or history of liver tumours (benign or malignant) (see section 4.4).
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal (see section 4.4).
- Pregnancy or suspected pregnancy and breastfeeding (see section 4.6).
- Genital bleeding of unknown aetiology (see section 4.4).
- Concomitant use of hormonal contraceptives

4.4 Special warnings and precautions for use

Medical examination/consultation

Prior to the initiation or reinstitution of this medicinal product, a complete medical history (including family history) must be taken. Blood pressure must be measured and a physical examination must be performed guided by the contraindications (see section 4.3) and warnings for use (see section 4.4). During treatment, periodic check-ups must be carried out according to standard clinical practice.

Pregnancy must be ruled out prior to administering or re-initiation of Ryeqo.

Risk of thromboembolic disorders

The use of medicinal products containing an estrogen and a progestogen increases the risk of arterial or venous thromboembolism (ATE or VTE) compared with no use.

The risk of ATE/VTE with this medicinal product has not been established. It contains doses of estrogen and progestogen lower than the doses used in combined hormonal contraceptives and are provided in combination with relugolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist that suppresses ovarian production of estrogen and progesterone. Estradiol levels with Ryeqo are in the range observed in the early follicular phase of the menstrual cycle (see section 5.1).

If an ATE/VTE occurs, treatment must be discontinued immediately. This medicinal product is contraindicated in women with past or present venous or arterial thromboembolic disease (see section 4.3).

Risk factors for venous thromboembolism (VTE)
The risk for venous thromboembolic complications in women using a product with an estrogen and progestogen may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see Table 1 below).

Table 1. Risk factors for VTE

Risk factor	Comment
Obesity (body mass index [BMI] over 30 kg/m^2)	Risk increases substantially as BMI rises.
Prolonged immobilisation, major surgery or major trauma	In these situations, it is advisable to discontinue use of the medicinal product (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation.
Positive family history (VTE) ever in a sibling or parent especially at a relatively early age e.g. before 50 years.	If a hereditary predisposition is suspected, the woman must be referred to a specialist for advice before using the medicinal product.
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
Increasing age	Particularly above 35 years.

The increased risk of thromboembolism in pregnancy, and particularly the 6-week period of the puerperium, must be considered (for information on "Pregnancy and lactation" see section 4.6).

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)
In the event of symptoms, women must be advised to get urgent medical attention and to inform the physician that she is taking this medicinal product.

Symptoms of deep vein thrombosis (DVT) can include:
- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or walking;
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:
- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may be associated with haemoptysis;
- sharp chest pain;
- severe light headedness or dizziness;
- rapid or irregular heartbeat.

Some of these symptoms (e.g. "shortness of breath", "coughing") are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Risk factors for arterial thromboembolism (ATE)
Epidemiological studies have associated the use of estrogen/progestogen products with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

The risk for arterial thromboembolic complications in women using a product with an estrogen and progestogen may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see Table 2 below).

Table 2. Risk factors for ATE

Risk factor	**Comment**
Increasing age	Particularly above 35 years.
Smoking	Women are to be advised not to smoke if they wish to use the medicinal product.
Hypertension	
Obesity (body mass index [BMI] over 30 kg/m^2)	Risk increases substantially as BMI increases.
Positive family history (ATE) ever in a sibling or parent especially at relatively early age e.g. before 50 years.	If a hereditary predisposition is suspected, the woman must be referred to a specialist for advice before using the medicinal product.
Migraine	An increase in frequency or severity of migraine during use of the medicinal product (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE
In the event of symptoms, women must be advised to get urgent medical attention and to inform the physician that she is taking this medicinal product.

Symptoms of a cerebrovascular accident can include:
- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding;
- sudden trouble seeing in one or both eyes;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack.

Symptoms of myocardial infarction can include:
- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;
- discomfort radiating to the back, jaw, throat, arm, stomach;
- feeling of being full, having indigestion or choking;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

<u>Risk of bone loss</u>

Following an initial non-clinically relevant decrease in bone mineral density (BMD), it stabilized after 12-24 weeks of treatment and thereafter remained stable (as measured up to 2 years). The mean decrease in BMD during the first year of treatment was 0.69%.
However, decreases of > 3% were seen in 21% of the patients. Therefore, a DXA scan is recommended after the first 52 weeks of treatment and as considered appropriate thereafter. Depending on the degree of change in BMD, the benefit and risks of this medicinal product may need to be reconsidered.

The benefits and risks of this medicinal productin patients with a history of a low trauma fracture or other risk factors for osteoporosis or bone loss, including those taking medicinal products that may affect BMD, should be considered prior to initiating treatment. It is recommended to perform a DXA

scan before commencing treatment in these patients. This medicinal product should not be initiated if the risk associated with BMD loss exceeds the potential benefit of the treatment (see section 4.2).

Liver tumours or liver disease

This medicinal product is contraindicated in women with liver tumours, benign or malignant; or liver disease as long as liver function values have not returned to normal (see section 4.3). Treatment must be discontinued if jaundice develops.

In clinical studies asymptomatic transient elevations of serum alanine aminotransferase (ALT) at least 3 times the upper limit of the reference range occurred in < 1% of participants treated with this medicinal product. Acute liver test abnormalities may necessitate the discontinuation of this medicinal product use until the liver tests return to normal.

Renal impairment

The exposure to relugolix is increased in patients with moderate or severe renal impairment (see section 5.2), although no dose adjustment is required (see section 4.2). The amount of relugolix removed by haemodialysis is unknown.

Change in menstrual bleeding pattern

Patients must be informed that treatment usually leads to a reduction in menstrual blood loss or amenorrhoea within the first 2 months of treatment.

Women receiving this medicinal product, for the treatment of uterine fibroids, were likely to have amenorrhoea (51.6%) or cyclic bleeding (15.4%), with the rest (31.9%) having an irregular bleeding pattern at the Week 24 assessment. Furthermore, at the Week 52 and Week 104 assessments 70.6%, and 58.3% of women respectively were likely to have amenorrhoea.
For those patients with endometriosis, the majority of patients (65.2%) were likely to have amenorrhoea at the Week 24 assessment, with a subsequent 76.6% at the Week 52 assessment and 82.3% at the Week 104 assessment.

In case of persistent excessive bleeding, patients must notify their physician.

Contraceptive properties

This medicinal productprovides adequate contraception when used for at least 1 month (see section 4.2). However, women of childbearing potential must be advised that ovulation will return rapidly after discontinuing treatment. Therefore, alternative contraception needs to be started immediately after discontinuation of treatment.

Reduced ability to recognise pregnancy

Women who take this medicinal product commonly experience amenorrhoea or a reduction in the amount, intensity, or duration of menstrual bleeding.

This change in menstrual bleeding pattern may reduce the ability to recognise the occurrence of a pregnancy in a timely manner. Perform pregnancy testing if pregnancy is suspected and discontinue treatment, if pregnancy is confirmed (see section 4.3).

Uterine fibroid prolapse or expulsion

Submucosal uterine fibroids are common (15% to 20% of women with uterine fibroids) and some may prolapse through the cervix or be expelled, sometimes with transient worsening of uterine bleeding. Women known or suspected to have submucosal uterine fibroids must be advised regarding the possibility of uterine fibroid prolapse or expulsion when treated, and should contact their physician if

severe bleeding reoccurs after bleeding symptoms have improved while being treated.

Depression

Women with a history of depression should be carefully monitored, and treatment should be discontinued if depression recurs to a serious degree.
Data are limited on the association of this or other products containing estradiol and progestins with onset of depression or exacerbation of existing depression. Women must be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Hypertension

Although small increases in blood pressure have been reported, clinically relevant increases are rare (see section 4.8). However, if sustained clinically significant hypertension develops during use, hypertension should be treated, and the benefit of continued therapy should be assessed. If treatment is discontinued, use may be resumed if normotensive values have been achieved with antihypertensive treatment.

Gallbladder disease

Conditions such as gallbladder disease, cholelithiasis and cholecystitis have been reported to occur or worsen with estrogen and progestogen use, including this medicinal product, but the evidence of an association with this medicinal product is inconclusive.

Laboratory tests

The use of estrogens and progestogens may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

Excipients with known effect

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

4.5 Interaction with other medicinal products and other forms of interaction

Recommendations regarding interactions with this medicinal product are based on evaluations of interactions for the individual components.

Potential for other medicinal products to affect the components of Ryeqo

Relugolix

Oral P-glycoprotein (P-gp) inhibitors
Concomitant use with oral P-gp inhibitors is not recommended. Relugolix is a substrate of P-gp (see section 5.2) and in an interaction study with erythromycin, a P-gp and moderate cytochrome P450 (CYP) 3A4 inhibitor, the area under the curve (AUC) and maximum concentration (C_{max}) of relugolix were increased by 4.1-fold and 3.8-fold, respectively. Concomitant use of P-gp inhibitors may increase

the exposure of relugolix, including certain anti-infective medicinal products (e.g. erythromycin, clarithromycin, gentamicin, tetracycline), anti-fungal medicinal products (ketoconazole, itraconazole), antihypertensive medicinal products (e.g. carvedilol, verapamil), antiarrhythmic medicinal products (e.g. amiodarone, dronedarone, propafenone, quinidine), antianginal medicinal products (e.g. ranolazine), cyclosporine, human immunodeficiency virus (HIV) or hepatitis C virus (HCV) protease inhibitors (e.g. ritonavir, telaprevir). If concomitant use with once or twice daily oral P-gp inhibitors is unavoidable (e.g. azithromycin), take Ryeqo first, and separate dosing with the P-gp inhibitor by at least 6 hours and monitor patients more frequently for adverse reactions.

Strong cytochrome P450 3A4 (CYP3A4) and/or P-gp inducers
Concomitant use with strong CYP3A4 and/or P-gp inducers is not recommended. In a clinical interaction study with rifampicin, a strong CYP3A4 and P-gp inducer, the C_{max} and AUC of relugolix were reduced by 23% and 55%, respectively. Medicinal products that cause strong CYP3A4 and/or P-gp induction, such as anticonvulsants (e.g. carbamazepine, topiramate, phenytoin, phenobarbital, primidone, oxcarbazepine, felbamate), anti-infective medicinal products (e.g. rifampicin, rifabutin, griseofulvin); St. John's wort (*Hypericum perforatum*); bosentan and HIV or HCV protease inhibitors (e.g. ritonavir, boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz), may reduce the plasma concentrations of relugolix and may result in a decrease in therapeutic effects.

CYP3A4 inhibitors
Concomitant use of relugolix with strong CYP3A4 inhibitors devoid of P-gp inhibition (voriconazole) did not increase the exposure of relugolix in a clinically meaningful manner. Furthermore, in a clinical interaction study, concomitant administration with atorvastatin, a weak CYP3A4 enzyme inhibitor, did not change the exposure of relugolix in a clinically meaningful manner.

Effect of co-administered medicinal products on relugolix exposure from clinical studies and recommendations are summarised in Table 3.

Table 3. Effect of co-administered medicinal products on relugolix exposure ($AUC_{0-\infty}$,C_{max}; in order of decreasing magnitude) from clinical studies and recommendations

Interacting drug dose regimen	Relugolix dose regimen	Change in relugolix $AUC_{0-\infty}$	Change in relugolix C_{max}	Recommendation
erythromycin 500 mg QID, multiple doses	40 mg single dose	4.1-fold ↑	3.8-fold ↑	Concomitant use with erythromycin and other oral P-gp inhibitors is not recommended. If concomitant use with once or twice daily oral P-gp inhibitors is unavoidable (e.g. azithromycin), Ryeqo should be taken first, followed by administration of the P-gp inhibitor at least 6 hours thereafter and monitor patients more frequently for adverse reactions.
azithromycin 500 mg single dose	120 mg single dose**	1.5-fold ↑	1.6-fold ↑	
azithromycin 500 mg single dose 6 hours after administration of relugolix		1.4-fold ↑	1.3-fold ↑	
voriconazole 200 mg BID, multiple doses	40 mg single dose	51% ↑	21% ↑	No dose modifications recommended for coadministration of relugolix and CYP3A4 inhibitors devoid of P-gp inhibition.
fluconazole	40 mg single dose	19% ↑	44% ↑	

200 mg QD, multiple doses				
atorvastatin 80 mg QD, multiple doses	40 mg single dose	5% ↓	22% ↓	
rifampicin 600 mg QD, multiple doses	40 mg single dose	55% ↓	23% ↓	Coadministration with rifampicin and other combined P-gp and strong CYP3A4 inducers is not recommended as the efficacy of the relugolix component of this medicinal product could be reduced.

* Data given as x-fold change represent a ratio between concomitant use and relugolix alone. Data given as % change represent % difference relative to relugolix alone.
** For further details check Orgovyx SmPC, effect for the 40 mg dose not investigated, but expected to be larger.
Increase is indicated as "↑", decrease as "↓".
AUC = area under curve; C_{max}= maximum concentration; QD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

Estradiol and norethisterone acetate

CYP3A4 inhibitors
Medicinal products that inhibit the activity of hepatic drug-metabolising enzymes, e.g. ketoconazole, may increase circulating concentrations of the estrogen and norethisterone components in Ryeqo.

CYP enzyme inducers
The metabolism of estrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).
Ritonavir, telaprevir and nelfinavir, although known as strong inhibitors, are also inducers and may decrease the exposure of estrogens and progestogens.
Herbal preparations containing St John's Wort (*Hypericum perforatum*) may induce the metabolism of estrogens and progestogens. Clinically, an increase in estrogen metabolism may lead to decreased effectiveness with regard to protection of bone loss. Therefore, long-term concomitant use of liver enzyme inducers with this medicinal product is not recommended.

Potential for the components of Ryeqo to affect other medicinal products

Relugolix
Relugolix is a weak inducer of CYP3A4. After concomitant use with daily 40 mg doses of relugolix, the AUC and C_{max} of midazolam, a sensitive CYP3A4 substrate, were decreased by 18% and 26%, respectively. However, based on the clinical study with midazolam, clinically meaningful effects of relugolix on other CYP3A4 substrates are not expected.

Relugolix is an inhibitor of breast cancer resistant protein (BCRP) *in vitro*, therefore, an interaction study was conducted with rosuvastatin, a BCRP and organic anion transporting polypeptide 1B1 (OATP1B1) substrate. After concomitant use with daily 40-mg doses of relugolix, the AUC and C_{max} of rosuvastatin were decreased by 13% and 23%, respectively. The effects are not considered clinically meaningful and therefore no dose-adjustments of rosuvastatin upon concomitant use are recommended. Clinical effects of this medicinal product on other BCRP substrates have not been evaluated and the relevance for other BCRP substrates is unknown.

Relugolix may cause saturation of intestinal P-gp at the 40 mg dose, as relugolix exhibits more than dose proportional pharmacokinetics over the dose range of 10-120 mg, which could result in increased absorption of co-administered medicines that are sensitive substrates of P-gp. No clinically significant differences in the pharmacokinetics of dabigatran etexilate (P-gp substrate) were observed upon concomitant use with relugolix, clinically meaningful effects of relugolix on other P-gp substrates are not expected.

Estradiol and norethisterone acetate
Estrogen and progestogen medicinal products may affect the metabolism of certain other active substances. Accordingly, plasma concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine) with use of Ryeqo. Dose adjustment of these medicinal products may be necessary.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Ryeqo inhibits ovulation in women taking the recommended dose and provides adequate contraception. A nonhormonal contraceptive method is recommended for use for 1 month after initiation of treatment and for 7 days following 2 or more missed consecutive doses. Concomitant use of hormonal contraceptives is contraindicated (see section 4.3).

Women of childbearing potential must be advised that ovulation will return rapidly after discontinuing Ryeqo. A discussion with the patient, regarding appropriate contraceptive methods, must therefore take place prior to discontinuing treatment and alternative contraception needs to be started immediately after discontinuation of treatment (see section 4.4).

Pregnancy

There is a limited amount of data from the use of relugolix in pregnant women. Studies in animals have shown that exposure to relugolix early in pregnancy may increase the risk of early pregnancy loss (see section 5.3). Based on the pharmacological effects, an adverse effect on pregnancy cannot be excluded.

Ryeqo is contraindicated during pregnancy (see section 4.3). Treatment should be discontinued if pregnancy occurs.

There appears to be little or no increased risk of harmful effects in children born to women who have used estrogens and progestogens as an oral contraceptive inadvertently during early pregnancy. The increased risk of VTE during the postpartum period must be considered when re-starting Ryeqo (see section 4.4).

Breast-feeding

Results from non-clinical studies indicate that relugolix is excreted into the milk of lactating rats (see section 5.3). No data are available regarding the presence of relugolix or its metabolites in human milk or its effect on the breastfed infant. Detectable amounts of estrogen and progestogens have been identified in the breast milk of women receiving estrogen plus progestogen therapy. An effect on breastfeeding newborns/infants cannot be excluded.

Breastfeeding is contraindicated during the use of Ryeqo (see section 4.3) and for 2 weeks following its discontinuation.

Fertility

Ryeqo inhibits ovulation and often causes amenorrhoea. Ovulation and menstrual bleeding will return rapidly after discontinuing treatment (see section 5.1).

4.7 Effects on ability to drive and use machines

This medicinal product has minor influence on the ability to drive and use machines. When driving vehicles or operating machines it should be taken into account that dizziness may occur occasionally.

4.8 Undesirable effects

Summary of the safety profile
The most frequent adverse reactions, in patients being treated for uterine fibroids or endometriosis, were headache (13.2%), hot flush (10.3%) and uterine bleeding (5.8%).

Adverse reactions listed in Table 4 are classified according to frequency and system organ class. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and not known (cannot be estimated from available data).

Tabulated list of adverse reactions

Table 4. Adverse reactions in patients with uterine fibroids and endometriosis

Psychiatric disorders	
Common	Irritability Libido decreased*
Nervous system disorders	
Very common	Headache
Common	Dizziness
Vascular disorders	
Very common	Hot flush
Rare	Hypertension
Gastrointestinal disorders	
Common	Nausea
Uncommon	Dyspepsia
Skin and subcutaneous tissue disorders	
Common	Alopecia Hyperhidrosis Night sweats
Uncommon	Angioedema Urticaria
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Reproductive system and breast disorders	
Common	Uterine bleeding** Vulvovaginal dryness
Uncommon	Breast cyst Uterine myoma expulsion

* includes libido decreased, libido loss and libido disorder.
** includes menorrhagia (heavy menstrual bleeding), metrorrhagia (intermenstrual bleeding), vaginal haemorrhage, uterine haemorrhage, polymenorrhoea, and menstruation irregular.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses of relugolix up to 360 mg (9 times the recommended clinical dose of 40 mg) have been administered to healthy men and women and were generally well tolerated.

Overdoses up to 2 times the recommended dose have been reported during the clinical development of relugolix in combination with estradiol and norethisterone acetate without reports of adverse events. Supportive care is recommended if an overdose occurs. The amount of relugolix, estradiol or norethisterone removed by haemodialysis is unknown.

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing medicinal products by young children. Overdose of estradiol and norethisterone acetate may cause nausea and vomiting, and withdrawal bleeding may occur in women.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, anti-gonadotrophin-releasing hormones, ATC code: H01CC54

Mechanism of action

Relugolix is a non-peptide GnRH receptor antagonist that binds to and inhibits GnRH receptors in the anterior pituitary gland. In humans, inhibition of GnRH receptor results in a dose dependent decrease in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are reduced. The reduction in FSH concentrations prevents follicular growth and development, thereby reducing the production of estrogen. Prevention of an LH surge inhibits ovulation and development of the corpus luteum, which precludes the production of progesterone. Therefore, this medicinal product provides adequate contraception when taken for at least 1 month (see section 4.2).

Estradiol is the same as the endogenously produced hormone and is a potent agonist of the nuclear estrogen receptor (ER) subtypes. Exogenously administered estradiol alleviates symptoms associated with a hypoestrogenic state, such as vasomotor symptoms and bone mineral density loss.

Norethisterone acetate is a synthetic progestogen. As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Pharmacodynamic effects

Effects on pituitary and ovarian hormones
After administration of relugolix, rapid, dose-dependent decreases in circulating concentrations of LH, FSH, and estradiol are observed. Near maximum decreases in estradiol concentrations is noted with a 40 mg dose to within the postmenopausal range. Across clinical studies, average estradiol concentrations were consistently maintained at least 10 pg/mL higher with Ryeqo compared with relugolix alone. In the phase 3 clinical studies, in patients with uterine fibroids, with Ryeqo, median

estradiol predose concentrations after 24 weeks were approximately 33 pg/mL, and in those with endometriosis were approximately 38 pg/mL corresponding with estradiol concentrations associated with the early follicular phase of the menstrual cycle. Progesterone levels in both populations were maintained at < 3.0 ng/mL with Ryeqo.

Effects on ovulatory function
In a single cohort study in healthy premenopausal women, administration of Ryeqo once daily for 84 days substantially suppressed follicular growth throughout the 84-day treatment period (mean dominant follicle size of approximately 6 mm) and ovulation was inhibited in 100% of women as assessed by the Hoogland-Skouby score. After discontinuation of treatment, all women assessed (66 of 67) returned to ovulation within 43 days (mean 23.5 days).

Uterine fibroids

Efficacy and safety over 24 weeks
The efficacy and safety of Ryeqo once daily in patients with uterine fibroids was assessed in two replicate, 24-week, multinational, randomised, double-blind, placebo-controlled studies in patients aged 18-50 years with heavy menstrual bleeding associated with uterine fibroids (Studies L1 and L2). Patients were required to have uterine fibroids confirmed by ultrasound and menstrual blood loss (MBL) volume of ≥ 80 mL, as assessed by the alkaline hematin method.

Both studies had 3 treatment groups: Women were randomised to receive relugolix 40 mg + estradiol 1 mg and norethisterone acetate 0.5 mg (E2/NETA) (Ryeqo) for 24 weeks, or placebo for 24 weeks, or relugolix 40 mg for 12 weeks followed by relugolix 40 mg co-administered with E2/NETA for 12 weeks. The median age of women was 42 years, and mean body mass index was 31.7 kg/m^2. Approximately 49.4% of women were Black, 44.7% were White, and 5.9% were of other races.

Reduction in heavy menstrual bleeding
In both studies, a statistically significant higher percentage of responders, defined as MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume, was observed in favour of women actively treated compared with placebo (Table 5). Reductions in MBL volume were seen as early as the first assessment (Week 4). The results for other secondary endpoints related to bleeding are as shown in Table 5. All key secondary endpoints were alpha -controlled.

Table 5. Results of primary and selected secondary efficacy assessments in study L1 and study L2 (uterine fibroids)

	Study L1		**Study L2**	
	Ryeqo (N = 128)	**Placebo (N = 127)**	**Ryeqo (N = 125)**	**Placebo (N = 129)**
Number (%) of responders[a,b]	94 (73.4%)	24 (18.9%)	89 (71.2%)	19 (14.7%)
Number (%) of patients with MBL < 80 mL	97 (75.8%)	34 (26.8%)	97 (73.6%)	25 (19.4%)
Number (%) of patients with ≥ 50% reduction in MBL volume	101 (78.9%)	28 (22.1%)	96 (76.8%)	28 (21.7%)
Number (%) of patients with amenorrhoea[b,c]	67 (52.3%)	7 (5.5%)	63 (50.4%)	4 (3.1%)
Number (%) of patients with > 1.24 mmol/L (2 g/dL) improvement in haemoglobin levels[d]	15 (50.0%)	5 (21.7%)	19 (61.3%)	2 (5.4%)
Number (%) of patients who achieved NRS ≤ 1[b,e]	25 (43.1%)	7 (10.1%)	32 (47.1%)	14 (17.1%)

Percent change in primary uterine fibroid volume	-12.4 (5.62)	-0.3 (5.40)	-17.4 (5.93)	-7.4 (5.92)
Percent change in uterine volume	-12.9 (3.08)	2.2 (3.01)	-13.8 (3.39)	-1.5 (3.37)

[a] A responder is defined as a woman who achieved both a MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment.
[b] p-value < 0.0001 is comparison of active treatment vs placebo stratified by baseline MBL volume (< 225 mL, ≥ 225 mL) and geographic region (North America, Rest of World).
[c] Amenorrhoea is defined as reported amenorrhoea, spotting, or negligible bleeding (MBL < 5 mL) with supporting eDiary compliance at 2 consecutive visits.
[d] In patients with a baseline Haemoglobin level ≤ 6.52 mmol/L (10.5 g/dL).
[e] In patients with moderate or severe pain at baseline.
Abbreviations: MBL = menstrual blood loss; NRS = numerical rating scale; UFSQoL = uterine fibroid symptom and quality of life.

Endometriosis

Efficacy and safety over 24 weeks
The efficacy and safety of Ryeqo once daily, in patients with endometriosis was assessed in two replicate, 24-week, multinational, randomised, double-blind, placebo-controlled studies in patients aged 18–50 years with moderate to severe pain associated with endometriosis (Studies S1 and S2). Patients were required to have endometriosis confirmed by direct visualisation during surgery and/or histological confirmation and were required to have moderate to severe pain as assessed based on an 11-point numerical rating scale (NRS).

Both studies had three treatment groups: Women were randomised to receive relugolix 40 mg + estradiol 1 mg and norethisterone acetate 0.5 mg (E2/NETA) (Ryeqo) for 24 weeks, or placebo for 24 weeks, or relugolix 40 mg for 12 weeks followed by relugolix 40 mg co-administered with E2/NETA for 12 weeks. Patients were eligible for inclusion if they had moderate to severe pain before the screening period until after the run- in period (i.e. at least two cycles). A high percentage (83.2%) of the study population of Studies S1 and S2 reported having undergone previous surgeries/procedures for endometriosis treatment. A low percentage (8%) of the study population did not report previous surgical or medical treatment before inclusion into the studies. At baseline, most patients (92.6%) used analgesics for pelvic pain, including 29.1% of patients in Study S1 and 48.4% of patients in Study S2 who used opioids. The most frequently reported other pharmacotherapies for endometriosis included dienogest (19.4%), estrogen progestin oral contraceptive (15.2%) and GnRH agonists (7.6%). The median age of women was 34 years, and mean body mass index was 26 kg/m^2. Approximately 91% of women were White, 6% were Black, and 3% were of other races.

Reduction in dysmenorrhoea and non-menstrual pelvic pain
Studies S1 and S2 had two co-primary endpoints, consisting of 2 responder analyses. In both studies, a statistically significantly higher percentage of responders was observed, defined as a reduction from baseline in dysmenorrhea of at least 2.8 points over the last 35 days of treatment, without an increase in analgesic use (ibuprofen or opioid), defined as a reduction from baseline in non-menstrual pelvic pain score of at least 2.1 points over the last 35 days of treatment, without an increase in analgesic use (ibuprofen or opioid) (Table 6).

Table 6. Results of co-primary efficacy assessments in study S1 and study S2 (endometriosis)

Endpoint definition	**Study S1**		**Study S2**	
	Ryeqo (N = 212)	**Placebo (N = 212)**	**Ryeqo (N = 206)**	**Placebo (N = 204)**
Number (%) of responders for dysmenorrhea[a,c]	158 (74.5%)	57 (26.9%)	155 (75.2%)	62 (30.4%)

Number (%) of responders for non-menstrual pelvic pain (NMPP)[b,c]	124 (58.5%)	84 (39.6%)	136 (66.0%)	87 (42.6%)

[a] Responders were patients whose NRS score for dysmenorrhea declined from baseline to Week 24/EOT by ≥ 2.8 points, and the patient did not have increased use of study-specified analgesics for pelvic pain at Week 24/EOT relative to baseline.
[b] Responders were patients whose NRS score for NMPP declined from baseline to Week 24/EOT by ≥ 2.1 points, and the patient did not have increased use of study specified analgesics for pelvic pain at Week 24/EOT relative to baseline.
[c] p-value < 0.0001 is comparison of Ryeqo vs placebo adjusted by baseline pain score, time since initial surgical diagnosis of endometriosis and geographic region.
Abbreviations: N = number of patients; NMPP = Non-menstrual pelvic pain; NRS = Numerical Rating Scale scores (0=no pain, 10=worst pain as bad as you can imagine).

The results for the key secondary efficacy endpoints are shown in Table 7. All key secondary endpoints were alpha controlled.

Table 7. Results of selected secondary efficacy assessments in study S1 and study S2 (endometriosis)

Endpoint definition	**Study S1**		**Study S2**	
	Ryeqo (N = 212)	**Placebo (N = 212)**	**Ryeqo (N = 206)**	**Placebo (N = 204)**
Change in the EHP-30 Pain Domain score, LS Mean (SE)[a,b]	-33.8 (1.83)	-18.7 (1.83)	-32.2 (1.68)	-19.9 (1.69)
Change in the mean dysmenorrhea NRS score, LS Mean (SE) [a,b]	-5.1 (0.19)	-1.8 (0.19)	-5.1 (0.19)	-2.0 (0.19)
Change in the mean NMPP NRS score, LS Mean (SE) [a,b]	-2.9 (0.18)	-2.0 (0.18)	-2.7 (0.17)	-2.0 (0.17)
Change in the mean dyspareunia NRS score, LS Mean (SE) [a,b]	-2.4 (0.21)	-1.7 (0.22)	-2.4 (0.19)	-1.9 (0.19)
Proportion of patients who are not using protocol-specified opioids for endometriosis-associated pain, n (%)[c]	182 (85.8%)	162 (76.4%)	169 (82.0%)	135 (66.2%)

[a] LS means were based on mixed-effects model with treatment, baseline value, visit, geographic region (North America, Rest of World), time since initial surgical diagnosis of endometriosis (< 5 years, ≥ 5 years), and treatment-by-visit interaction included as fixed effects; visit was also included in the model as random effect within each patient, and an unstructured covariance matrix was assumed.
[b] Change from baseline to Week 24//EOT
[c] At Week 24/EOT
Abbreviations: EOT = end-of-treatment; LS = least square; N = number of patients; NETA = norethisterone acetate; NMPP = non-menstrual pelvic pain; NRS = Numerical Rating Scale, SE = standard error.

Bone mineral density (BMD) measurements over 104 weeks
The effect on BMD was evaluated by DXA at week 12, 24, 36, 52 and 104. A total of 477 women with uterine fibroids who completed the 24-week pivotal studies (Study L1 and L2) were enrolled into a 28 week, open-label, single arm extension study (Study L3), where all women received Ryeqo. A

total of 228 women who completed the extension study were enrolled into an additional 52 week study (randomised withdrawal study) where they were re randomised to receive either Ryeqo or placebo A total of 802 women with endometriosis who completed the 24-week pivotal studies (Study S1 and S2) were enrolled into the extension study (Study S3), where all patients received Ryeqo.
BMD measurements over 104 weeks in patients with uterine fibroids and endometriosis are summarised in Table 8.

Table 8. Bone mineral density (BMD) measurements over 104 weeks in patients with uterine fibroids and endometriosis

	Ryeqo (N = 672)	**Placebo (N = 672)**
Lumbar spine (L1 – L4)		
Study L1 & L2, S1 & S2		
Week 12		
N	553	545
LS means % change[a]	-0.56	0.15
(95% CI)	(-0.77, -0.36)	(-0.05, 0.36)
Week 24		
N	528	516
LS means % change[a]	-0.59	0.13
(95% CI)	(-0.82, -0.37)	(-0.09, 0.36)
Study L3 and S3	**Ryeqo**	**Placebo → Ryeqo**
Week 36		
N	387	379
LS means % change[a]	-0.66	-0.00
(95% CI)	(-0.93; -0.40)	(-0.27; 0.26)
Week 52		
N	365	351
LS means % change[a]	-0.69	-0.30
(95% CI)	(-1.00; -0.38)	(-0.61; 0.01)
Randomised withdrawal study and Study S3	**Ryeqo**	**Placebo[b]**
Week 104		
N	221	229
LS means % change[a]	-0.40	-0.18
(95% CI)	(-0.82; 0.02)	(-0.60; 0.23)

Abbreviations: LS mean = least squares mean; CI = confidence interval, N = number of patients
[a] % change from baseline;
[b] Majority of the patients randomised to the placebo group in the randomised withdrawal study were actively treated within about 2 cycles upon reassumption of HMB.

In the Ryeqo group, LS mean percent changes from baseline in BMD to week 52 and week 104 at the lumbar spine were -0.69% and -0.40%, respectively.

Over a period of 12 months after cessation of Ryeqo, in those endometriosis patients who met BMD loss criteria, evidence of recovery or trend towards recovery was observed in 100% of women at the lumbar spine.

BMD measurements over 12 weeks in women with uterine fibroids and endometriosis treated with relugolix monotherapy

In women treated with relugolix monotherapy for 12 weeks, in studies L1 and L2, S1 and S2, BMD at the lumbar spine decreased by -1.86% from baseline. The difference in percent change in BMD between women treated with Ryeqo and relugolix monotherapy at Week 12 was statistically significant, demonstrating the effectiveness of using relugolix in combination with E2/NETA (Ryeqo) to mitigate bone loss.

To provide context for the effects of Ryeqo on percent change in BMD over 52 weeks treatment, an observational study of untreated age-matched women with uterine fibroids and endometriosis was conducted to characterise longitudinal BMD of premenopausal women aged 18-50 years (natural history study). Through 52 weeks of observation, there was minimal change in BMD with Ryeqo compared with those in an age-matched cohort of premenopausal women with uterine fibroids and endometriosis.

Effects on endometrium
In the clinical studies, no cases of endometrial hyperplasia or endometrial carcinoma assessed by biopsy were observed in women treated with Ryeqo for up to 52 weeks.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Ryeqo in all subsets of the paediatric population in treatment of leiomyoma of the uterus or endometriosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of relugolix, estradiol (E2), total estrone (E1), and norethisterone (NET) following oral administration of a single Ryeqo tablet to healthy postmenopausal women under fasted conditions are summarized in Table 9.

Table 9. Single dose pharmacokinetic parameters of relugolix, estradiol, total estrone, and norethisterone in post-menopausal women

	Relugolix	Estradiol (E2)	Unconjugated Estrone (E1)	Norethisterone (NET)
$AUC_{0-\infty}$ (ng*hr/mL or pg*hr/mL)	198.1 (111.6)	818.7 (334.4)	4126 (1650)	17.5 (8.46)
C_{max} (ng/mL or pg/mL)	25.99 (18.21)	27.95 (19.15)	188.4 (59.09)	3.57 (1.43)
T_{max} (hr)	2.00 (0.25, 5.00)	7.00 (0.25, 24.00)	6.00 (2.00, 12.00)	1.01 (0.50, 4.00)
Terminal $t_{1/2}$ (hr)	61.5 (13.2)	16.6 (7.67)	15.9 (6.52)	10.9 (3.05)

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; C_{max} = maximum observed concentration; E1 = estrone; E2 =estradiol; NET = norethisterone; T_{max} = time to the maximum observed concentration; $t_{1/2}$ = half-life
Note: Baseline-adjusted pharmacokinetic parameters for estradiol and unconjugated E1 are presented in this table. Arithmetic means and standard deviations are shown except for t_{max}, where median and range (minimum, maximum) are shown. $AUC_{0-\infty}$ is presented in ng*hr/mL for relugolix and NET and in pg*hr/mL for unconjugated E2 and unconjugated E1. C_{max} is presented in ng/mL for relugolix and NET and in pg/mL for unconjugated E2 and unconjugated E1.

The pharmacokinetic parameters of relugolix, estradiol (E2), total estrone (E1), and norethisterone (NET) at steady state after once daily administration of Ryeqo for 6 weeks to healthy premenopausal women are summarized in Table 10.

Table 10. Multi-dose pharmacokinetic parameters of relugolix, estradiol, total estrone, and norethisterone in pre-menopausal women

	Relugolix	Estradiol (E2)	Unconjugated Estrone (E1)	Norethisterone (NET)
AUC_{0-24} (ng*hr/mL or pg*hr/mL)	157 (94.7)	784 (262)	4 450 (1 980)	25.5 (11.4)
C_{max} (ng/mL or pg/mL)	26 (21.4)	46.8 (17.3)	303 (137)	5.21 (1.53)
T_{max} (hr)	3 (0.5, 6)	3 (0.50, 12.00)	4 (1, 8.08)	1 (1, 2)
Effective $t_{1/2}$ (hr)	~25	17.1 (4.03)	13.9 (4.14)	8.28 (1.87)

Abbreviations: AUC_{0-24} = area under the concentration-time curve during a dosing interval (24); C_{max} = maximum observed concentration; E1 = estrone; E2 =estradiol; NET = norethisterone; t_{max} = time to the maximum observed concentration.
Note: arithmetic means and standard deviations are shown except for t_{max}, where median and range (minimum, maximum) are shown. AUC_{0-24} is presented in ng*hr/mL for relugolix and NET and in pg*hr/mL for unconjugated E2 and unconjugated E1. C_{max} is presented in ng/mL for relugolix and NET and in pg/mL for unconjugated E2 and unconjugated E1. Effective half-life for relugolix is estimated from accumulation ratios based on AUC values after multiple-dose administration of relugolix at 40 mg.

Absorption

The absorption of relugolix after oral administration is primarily mediated by the P-gp efflux transporter, for which relugolix is a substrate. After oral administration, relugolix is rapidly absorbed, reaching an initial peak by 0.25 hours postdose followed by one or more subsequent absorption peaks through up to 12 hours postdose. The absolute bioavailability of relugolix is 11.6%. After administration of Ryeqo with a high-fat, high-calorie meal, the $AUC_{0-\infty}$ and C_{max} of relugolix were decreased by 38% and 55%, respectively, compared with the fasted state.

After oral administration of a single dose of Ryeqo in the fasted state, unconjugated estradiol concentrations increased slowly with mean concentrations reaching peak concentrations at 8 hours postdose. After administration of Ryeqo following consumption of a high-fat, high-calorie meal, no clinically meaningful effects of food on the exposure to estradiol or estrogenic metabolites were observed.

After oral administration, norethisterone acetate undergoes rapid biotransformation in the intestine and liver to norethisterone (NET). After oral administration of a single dose of Ryeqo in the fasted state, NET concentrations were initially quantifiable at 0.5 hours postdose, increasing rapidly thereafter with mean concentrations reaching peak concentrations within 1 hour.

Food effects
Administration with food reduced the AUC and C_{max} of relugolix by 38% and 55%, respectively, relative to fasted conditions; however, the decrease in exposure to relugolix is considered not to be clinically meaningful. No clinically meaningful effects of food on the exposure to estradiol, estrogenic metabolites, or norethisterone were observed.

Distribution

Relugolix is 68% to 71% bound to human plasma proteins with a mean whole blood-to-plasma ratio of 0.78. Estradiol and norethisterone circulating in the blood bind to a similar extent to sex hormone-binding globulin (SHBG; 36% to 37%) and to albumin (61%), while only approximately 1-2% are unbound. The value for apparent volume of distribution (Vz) of 19×10^3 L derived from the absolute bioavailability study after intravenous administration indicates that relugolix distributes widely into tissues. The distribution of exogenous and endogenous estradiol is similar. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs.

Biotransformation

In vitro studies indicate that the primary CYP enzymes contributing to the overall hepatic oxidative metabolism of relugolix were CYP3A4/5 (45%) > CYP2C8 (37%) > CYP2C19 (< 1%) with the oxidative metabolites, metabolite-A and metabolite-B, formed by CYP3A4/5 and CYP2C8, respectively.

The metabolism of exogenous and endogenous estradiol is similar. Metabolism of estradiol occurs mainly in the liver and the gut but also in target organs and involves the formation of less active or inactive metabolites, including estrone, catecholestrogens and several estrogen sulphates and glucuronides. Estrogens are excreted with the bile, hydrolysed and reabsorbed (enterohepatic circulation), and mainly eliminated in urine in biologically inactive form. Oxidation of estrone and estradiol involves cytochrome P450 enzymes, mainly CYP1A2, CYP1A2 (extra hepatic), CYP3A4, CYP3A5, and CYP1B1 and CYP2C9.

The most important metabolites of norethisterone are isomers of 5alpha-dihydro-norethisterone and tetrahydro-norethisterone, which are excreted mainly in the urine as sulphate or glucuronide conjugates.

Elimination

Once absorbed, approximately 20% of relugolix is eliminated as unchanged active substance in the urine and 80% is eliminated through metabolism by multiple minor metabolic pathways and/or biliary secretion of unchanged active substance. Approximately 38% of the administered dose is excreted as metabolites (other than metabolite-C) in the faeces and urine. Metabolite-C, which is formed by intestinal microflora, is the primary metabolite in faeces (51%) and further reflects non-absorbed active substance.

The mean terminal phase elimination half-life ($t_{1/2}$) of relugolix, estradiol, and norethisterone following single-dose administration of the Ryeqo tablet are 61.5 hours, 16.6 hours, and 10.9 hours, respectively. Steady state of relugolix is reached after 12 to 13 days of once daily administration. The degree of accumulation of relugolix upon once daily administration is approximately 2-fold, reflecting an effective half-life of approximately 25 hours and supporting once daily administration of relugolix.

The accumulation for E2 and NET upon once daily administration are reported to be 33% to 47%, although when co-administered with relugolix, a weak inducer of intestinal (pre-systemic) CYP3A-mediated metabolism, the accumulation for E2 is expected to be similar or slightly lower.

Linearity/non-linearity

Relugolix is associated with greater than proportional increases in exposure with respect to dose, within the dose range from 1 to 80 mg, which is most pronounced at doses greater than 20 mg; and thought to be related to the saturation of intestinal P-gp, resulting in an increase in oral bioavailability. The pharmacokinetics of relugolix upon once daily administration of 40 mg relugolix is time independent.

Special populations

The single-dose pharmacokinetic parameters were not different between Japanese and Caucasian healthy subjects, indicating absence of ethnic sensitivity on the pharmacokinetics of relugolix. Population PK analysis suggests that there are no clinically meaningful differences in exposure of relugolix based on age, race or ethnicity, weight, or BMI. As both estradiol and norethisterone acetate are well known components of hormonal combination products, no studies in special populations were conducted.

Renal impairment
After administration of a single 40 mg dose of relugolix to patients with severe renal impairment, the exposure $AUC_{0-\infty}$ and C_{max} of relugolix were increased by 1.5- and 1.1-fold, respectively, compared with healthy control subjects with normal renal function. After administration of a single 40-mg dose of relugolix to patients with moderate renal impairment, the exposure $AUC_{0-\infty}$ and C_{max} of relugolix both were increased by 1.5-fold compared with healthy control subjects with normal renal function. Mild renal impairment was not a significant covariate for any of the pharmacokinetic parameters of relugolix in a population pharmacokinetic model. Although caution should be used to treat patients with moderate or severe renal impairment (see section 4.4), no dose adjustments in patients with mild, moderate or severe renal impairment are required (see section 4.2).
The effect of end-stage renal disease with or without haemodialysis on the pharmacokinetics of estradiol, norethisterone and relugolix, the components of Ryeqo, in premenopausal women have not been evaluated. The amount of relugolix, estradiol or norethisterone removed by haemodialysis is unknown.

Hepatic impairment
This medicinal product must not be used in patients with severe hepatic impairment (see section 4.3). No dose adjustments in patients with mild or moderate hepatic impairment are required (see section 4.2). After administration of a single 40-mg dose of relugolix to patients with mild hepatic impairment, the $AUC_{0-\infty}$ and C_{max} of relugolix were decreased by 31% and 24%, respectively, compared with healthy control subjects with normal hepatic function. After administration of a single 40-mg dose of relugolix to patients with moderate hepatic impairment, the $AUC_{0-\infty}$ and C_{max} of relugolix were decreased by 5% and increased by 1.2-fold, respectively, compared with healthy control subjects with normal hepatic function.

5.3 Preclinical safety data

Non-clinical studies have not been conducted with relugolix in combination with estradiol and norethisterone acetate. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

Reproductive toxicity and development

In pregnant rabbits orally dosed with relugolix during the period of organogenesis, spontaneous abortion and total litter loss were observed at exposure levels (AUC) comparable to that achieved at the recommended human dose of 40 mg/day. No effects on embryofoetal development were observed in rats; however, relugolix does not interact significantly with GnRH receptors in that species.

In experimental animals, estradiol or estradiol valerate displayed an embryo lethal effect already at relatively low doses; malformations of the urogenital tract and feminisation of male foetuses were observed.
Norethisterone, like other progestogens, caused virilisation of female foetuses in rats and monkeys. After high doses of norethisterone, embryo lethal effects were observed.

Lactation

In lactating rats administered a single oral dose of 30 mg/kg radiolabelled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose decreasing to low levels by 48 hours post-dose. The majority of relugolix-derived radioactivity in milk consisted of unchanged relugolix.

Environmental risk assessment (ERA)

Environmental risk assessment studies have shown that this medicinal product may pose a risk for the aquatic compartment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol (E 421)
Sodium starch glycolate
Hydroxypropylcellulose (E 463)
Magnesium stearate (E 572)
Hypromellose type 2910 (E 464)
Titanium dioxide (E 171)
Triacetin (E 1518)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Bottle
High-density polyethylene (HDPE) bottles with desiccant, closed with an induction-sealed child-resistant polypropylene cap containing 28 film-coated tablets. Each pack contains 28 or 84 film-coated tablets.

Blister
PVC/Al blister with desiccant packed in PET/Al/PE triplex foil sachet containing 14 film-coated tablets. Each pack contains 28 or 84 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1565/001

EU/1/21/1565/002
EU/1/21/1565/003
EU/1/21/1565/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 July 2021
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ryeqo 40 mg/1 mg/0.5 mg film-coated tablets
relugolix/estradiol/norethisterone acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg relugolix, 1 mg estradiol (as hemihydrate) and 0.5 mg norethisterone acetate.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 film-coated tablets
3×28 film-coated tablets
28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1565/001	28
EU/1/21/1565/002	84 (3 packs of 28)
EU/1/21/1565/003	28
EU/1/21/1565/004	84

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ryeqo

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

SACHET

1. NAME OF THE MEDICINAL PRODUCT

Ryeqo 40 mg/1 mg/0.5 mg film-coated tablets
relugolix/estradiol/norethisterone acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg relugolix, 1 mg estradiol (as hemihydrate) and 0.5 mg norethisterone acetate.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1565/003 28
EU/1/21/1565/004 84

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ryeqo 40 mg/1 mg/0.5 mg film-coated tablets
relugolix/estradiol/norethisterone acetate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.→Tue.→Wed.→Thu.→Fri.→Sat.→Sun.→....→Sun.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ryeqo 40 mg/1 mg/0.5 mg film-coated tablets
relugolix/estradiol/norethisterone acetate

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

28 tablets

6. OTHER

Also contains lactose monohydrate. See leaflet for further information.

Do not swallow the desiccant.

Gedeon Richter Plc.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ryeqo 40 mg/1 mg/0.5 mg film-coated tablets
relugolix/estradiol/norethisterone acetate

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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ryeqo is and what it is used for

Ryeqo contains the active substances relugolix, estradiol and norethisterone acetate.

It is used to treat
- moderate to severe symptoms of uterine fibroids (commonly known as myomas), which are non-cancerous tumours of the uterus (womb).
- symptoms associated with endometriosis in women with a history of previous medical or surgical treatment for their endometriosis (endometriosis is an often painful disorder in which tissue similar to the tissue that normally lines the inside of your uterus - the endometrium - grows outside your uterus).

Ryeqo is used in adult women (over 18 years of age) before they reach menopause.

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 to stop or reduce bleeding and to decrease pain and pelvic discomfort associated with uterine fibroids.

Women with endometriosis can experience pelvic or lower abdominal pain, pain with menstrual periods and pain with intercourse. Ryeqo is used for the treatment of endometriosis to decrease the symptoms due to displaced tissue of the lining of the womb.

This medicine contains relugolix, which blocks certain receptors in the brain, and this reduces the production of hormones that in turn stimulate the ovaries to produce estradiol and progesterone. When blocked, the levels of estrogen and progesterone circulating 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. What you need to know before you take Ryeqo

Do not take Ryeqo
Do not take Ryeqo if you have any of the conditions listed below.
If you do have any of the conditions listed below, you must tell your doctor:
- if you are **allergic** to relugolix, estradiol, norethisterone acetate or any of the other ingredients of this medicine (listed in section 6).
- if you have or previously have 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 parts of the body.
- if you have or previously have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke** or **angina**.
- if you have a **blood clotting disorder** (such as protein C deficiency, protein S deficiency, antithrombin-III deficiency, or Factor V Leiden).
- if you have **osteoporosis**.
- if you suffer from **headaches** with focal neurological symptoms such as paralysis or loss of muscle control, or **migraines** with visual disturbance.
- if you have any type of **cancer** which might be made worse by exposure to female sex hormones, such as **cancer of the breast or the genital organs**.
- if you have or ever had **liver tumours**.
- if you have or ever had a **liver disease** and your **liver function tests** have not returned to normal.
- if you are **pregnant** or if you think you **might be pregnant** or if you are **breastfeeding**.
- if you have any **genital bleeding** of unknown origin.
- if you are taking **hormonal contraception** (for example birth control pills) and unwilling to discontinue its use.

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

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

Warnings and precautions
Talk to your doctor or pharmacist before taking Ryeqo.

You should know that most women have reduced or no menstrual bleeding (period) 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 make sure you are not pregnant. You may also need a physical examination and additional checks, such as breast examination and a scan to measure how strong your bones are, that will be specific to your medical needs and/or concerns.

Stop taking Ryeqo and get urgent medical attention if you notice:
- any of the conditions mentioned in the “Do not take Ryeqo” section.
- if you notice signs of **liver disease:**
  - yellowing of your skin or the whites of your eyes (jaundice).
  - nausea or vomiting, fever, severe tiredness.
  - dark urine, itching or upper abdominal pain.
- a large rise in your **blood pressure** (symptoms may be headache, tiredness, dizziness).
- **migraine** for the first time or unusually bad **headaches** occurring more often than before.
- if you notice possible signs of a **blood clot** that may mean you are suffering from a clot in the leg (i.e. deep vein thrombosis), or in the lung (i.e. pulmonary embolism), a heart attack or a stroke. For a description of the symptoms of these serious conditions please go to ‘Ryeqo and risk of blood clots’.
- if you become **pregnant**.

Tell your doctor if any of the following conditions apply to you:
- if you have one or more of the **risk factors for developing a blood clot** listed below.

- if you have **high blood pressure**.
- if you have **osteoporosis**.
- if you suffer from **migraines**.
- if 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 recognise pregnancy.
- if you have or previously suffered from **depression**.
- if you have **renal (kidney) disease**.

Ryeqo and risk of blood clots
The use of other medicines containing an estrogen and a 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 your vein and/or artery:
- as you get **older** (particularly above about 35 year of age).
- if you are overweight (body mass index **> 30 kg/m^2**).
- if you have had **major surgery** or **prolonged time off your feet** (e.g. your leg is in a cast).
- if you have **recently given birth**.
- if anyone in your close family has had a **blood clot in the leg, lung or other organ**, a **heart attack** or a **stroke at a young age** (e.g. below the age of 50 years).
- if you **smoke**.
- if you have a problem with your heart (**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 affecting your natural defence system), **sickle cell disease** (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 factors you have.

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

*Symptoms of a blood clot in your leg (**deep vein thrombosis; DVT**)*
The symptoms of a blood clot in the leg known as a deep vein thrombosis (DVT) can include:
- swelling in your leg and/or foot or along a vein in your leg.
- pain or tenderness in your leg which feels worse when you stand up or are walking.
- increased heat in the affected leg with red or discoloured skin.

*Symptoms of a blood clot in your lung (**pulmonary embolism; PE**)*
The symptoms of a blood clot in the lung known as a pulmonary embolism (PE) can include:
- a sudden onset of unexplained shortness of breath or rapid breathing.
- sudden coughing which may be associated to a sharp pain in your chest.
- coughing up of blood.
- severe dizziness or feeling lightheaded.
- a rapid 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 squeezing or fullness in your chest, arm, or below your breastbone.
- discomfort radiating to your back, jaw, throat, arm, stomach.
- feeling of being full, having indigestion or choking.
- sweating, nausea, vomiting or dizziness.
- extreme weakness, anxiety, or shortness of breath.
- rapid or irregular heartbeats.

*Symptoms of a **stroke***
The symptoms of a stroke can include:
- a sudden numbness or weakness in your face, arm of leg, especially on one side of your body.
- sudden trouble walking, dizziness, loss of balance or coordination.
- sudden confusion, trouble speaking or understanding others.
- sudden trouble seeing in one or both of your eyes.
- sudden, severe or prolonged headache with no known cause.
- loosing consciousness or fainting with or without a seizure.

Surgery
If you are going to have surgery, tell the surgeon that you are taking Ryeqo.

Liver tumours or liver disease
In rare cases liver tumours or liver disease has been reported in women taking estrogens and progestogens. If you experience any symptoms of jaundice contact your doctor for further medical advice.

Renal (kidney) impairment
If you experience any decrease in urine production or notice any fluid retention causing swelling in your legs, ankles or feet, please contact your doctor for further medical advice.

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') within 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 contact your doctor for further medical advice.

Increased 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, contact your doctor for further medical advice.

Uterine fibroid prolapse and expulsion
Uterine fibroids may develop anywhere within the muscular wall of the uterus, including the submucosa, a thin layer of tissue in the uterus. In some women, the uterine fibroid may protrude or slip through the cervix into the vagina and may lead to significant worsening of uterine bleeding or pain. If you re-experience severe uterine bleeding after your symptoms have improved while being treated with Ryeqo, contact your doctor for medical advice.

Gallbladder disorders
Some women taking estrogen and progestogen hormones including Ryeqo have reported gallbladder disorders (gallstones or inflammation of your gallbladder). If you experience unusually severe pain below your rib cage or in your upper abdomen contact your doctor for medical advice.

Children and adolescents
Ryeqo should not be taken by children under 18 years of age since the safety and efficacy of Ryeqo has not been established in this age group.

Other medicines and Ryeqo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

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

- Certain medicines used to treat **epilepsy** (e.g. carbamazepine, topiramate, phenytoin, phenobarbital, primidone, oxcarbazepine, felbamate).
- Certain medicines used to treat human immunodeficiency virus infection/ acquired immunodeficiency syndrome **(HIV/AIDS)** (e.g. ritonavir, efavirenz).
- Certain medicines used to treat **Hepatitis C virus (HCV)** (e.g. boceprevir, sofosbuvir, velpatasvir, voxilaprevir, telaprevir, glecaprevir).
- Certain medicines used to treat **fungal infections** (e.g. ketoconazole, itraconazole, fluconazole, griseofulvin).
- Certain medicines used to treat **bacterial infections** (e.g. rifampicin, rifabutin, clarithromycin, erythromycin, gentamicin, tetracycline, griseofulvin).
- Certain medicine used to treat **high blood pressure in the arteries in the lung** (e.g. bosentan).
- Certain medicines used to treat **high blood pressure** (e.g. diltiazem, carvedilol, verapamil).
- Certain medicines used to treat **irregular heartbeats** (e.g. amiodarone, dronedarone, propafenone, quinidine, verapamil).
- Certain medicines used to treat **angina** (e.g. ranolazine, carvedilol, verapamil).
- Certain medicines to prevent organ rejection **after transplantion** (e.g. cyclosporine).
- Herbal remedies containing **St John's wort** (*Hypericum perforatum*).

Pregnancy and breast-feeding
Do not take Ryeqo if you are pregnant or breast-feeding. If you think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. If you become pregnant, stop taking Ryeqo and contact your doctor.

Ryeqo stops ovulation and thus you are not likely to become pregnant while using Ryeqo if used as recommended. Ovulation and menstrual bleeding will return rapidly after discontinuing Ryeqo and alternative birth control needs to be started immediately after discontinuation of Ryeqo.

Depending on when in your cycle you start taking Ryeqo, it may take time to obtain the full inhibition of ovulation by Ryeqo; therefore, nonhormonal birth control (e.g. condoms) should be used for the first month after starting Ryeqo.

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

Driving and using machines
Ryeqo has no known effect on the ability to drive and use machines.

Laboratory tests
If you need a blood or urine test, tell your doctor or the laboratory staff that you are taking Ryeqo because this medicine can affect the results of some tests.

Ryeqo contains lactose and sodium
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 essentially 'sodium-free'.

3. How to take Ryeqo

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet per day.

The tablet must be taken orally every day, at about the same time, with or without food with a little liquid.

It is recommended that you start taking Ryeqo within the first 5 days after the start of bleeding due to your period. If you start at another time of your menstrual cycle, you may initially experience irregular or heavier bleeding.

If you take more Ryeqo than you should
There have been no reports of serious harmful effects from taking several doses of this medicine at once. Large doses of estrogen may cause nausea and vomiting, and vaginal bleeding. If you have taken too many Ryeqo tablets ask your doctor or pharmacist for advice.

If you forget to take Ryeqo
If you miss one tablet, take it as soon as you remember and then resume taking your tablet the next day as usual. Do not take a double dose to make up for a forgotten tablet.

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

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

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.

Get urgent medical attention if you get any of the following signs and symptoms of an angioedema (allergic reaction):
- rapid swelling under the skin in areas such as the face, throat, arms and legs which can be life threatening if throat swelling blocks the airway.

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

Very common side effects (may affect more than 1 in 10 people)
- headache,
- hot flush.

Common side effects (may affect up to 1 in 10 people):
- irritability,
- decreased interest in sex,
- dizziness,
- nausea,
- hair loss,
- increased sweating,
- night sweats,
- joint pain,
- excessive, irregular, or prolonged bleeding from the womb (uterine bleeding),
- dryness of the genital area.

Uncommon side effects (may affect up to 1 in 100 people):
- indigestion,
- hives (urticaria),
- angioedema (rapid swelling under the skin in areas such as the face, throat, arms and legs),
- a lump in the breast tissue (breast cyst),

- uterine myoma expulsion (fibroid comes out either completely or partially through the vagina, usually with increased bleeding from the vagina).

Rare side effects (may affect up to 1 in 1 000 people):
- high blood pressure.

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 national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ryeqo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on both the outer carton and bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage condition.

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 Ryeqo contains
- The active substances are relugolix, estradiol and norethisterone acetate. One film-coated tablet contains 40 mg relugolix, 1 mg estradiol and 0.5 mg norethisterone acetate.
- The other ingredients are lactose monohydrate, mannitol (E 421), sodium starch glycolate, hydroxypropyl cellulose (E 463), magnesium stearate (E 572), hypromellose type 2910 (E 464), titanium dioxide (E 171), triacetin (E 1518), iron oxide yellow (E 172). See section 2 ‘Ryeqo contains lactose and sodium’.

What Ryeqo looks like and contents of the pack
Ryeqo is light yellow to yellow, round, film-coated tablet of 8 mm with “415” on one side, and plain faced on the other side.
Ryeqo is available in high-density polyethylene (HDPE) bottles with desiccant, closed with an induction-sealed child-resistant polypropylene cap or PVC/Al blister with desiccant packed in PET/Al/PE triplex foil sachet.
Each pack contains one or three bottles with 28 tablets each; or two or six blisters with 14 tablets each.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.