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 76 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Round, yellow to light yellow film-coated tablet, debossed 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.

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.

Posology

One tablet of Ryeqo must be taken once daily, at about the same time with or without food. Tablets should be taken with some liquid as needed (see section 5.2).

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).

Initiation of treatment
Pregnancy must be ruled out prior to initiating treatment with Ryeqo.

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.

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.

Contraceptive properties of Ryeqo

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 of Ryeqo.

After at least one month of Ryeqo use, Ryeqo inhibits ovulation in women taking the recommended dose 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 tablets

If one tablet is missed, the missed tablet must be taken as soon as possible and then continue the next day by taking a tablet at the usual time.

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).

Special populations

Elderly
There is no relevant use of Ryeqo in the elderly population in the indications.

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

Hepatic impairment
No dose adjustment for Ryeqo in patients with mild or moderate hepatic impairment is required (see section 5.2). Ryeqo 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. Tablets should be taken with some liquid as needed.

4.3. Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Venous thromboembolic disorder, past or present (e.g. deep venous thrombosis, pulmonary embolism).
- Arterial thromboembolic cardiovascular disease, past or present (e.g. myocardial infarction, cerebrovascular accident, ischemic heart disease).
- 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.
- 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.
- Pregnancy or suspected pregnancy and breastfeeding (see section 4.6).
- Genital bleeding of unknown aetiology.
- Concomitant use of hormonal contraceptives.

4.4. Special warnings and precautions for use

Ryeqo must only be prescribed after careful diagnosis.

Medical examination/consultation

Prior to the initiation or reinstitution of Ryeqo, 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.

Any hormonal contraception needs to be stopped prior to initiation of Ryeqo (see section 4.3). Nonhormonal methods of contraception must be used for at least 1 month after initiation of treatment. 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 Ryeqo has not been established. Ryeqo 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. Ryeqo 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 Ryeqo.

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 Ryeqo.

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.

Risk of bone loss

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 with Ryeqo 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 Ryeqo may need to be reconsidered.

The benefits and risks of Ryeqo in patients with a history of a low trauma fracture or other risk factors for osteoporosis or bone loss, including those taking medications that may affect BMD, should be considered prior to initiating treatment. It is recommended to perform a DXA scan before commencing treatment with Ryeqo in these patients. Ryeqo should not be initiated if the risk associated with BMD loss exceeds the potential benefit of the treatment.

Liver tumours or liver disease

Ryeqo 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 trials, 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 Ryeqo. Acute liver test abnormalities may necessitate the discontinuation of Ryeqo 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 with Ryeqo usually leads to a reduction in menstrual blood loss or amenorrhoea within the first 2 months of treatment.

Women receiving Ryeqo, 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 receiving Ryeqo 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 of Ryeqo

Ryeqo provides 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 Ryeqo 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.

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 with Ryeqo, and should contact their

physician if severe bleeding reoccurs after bleeding symptoms have improved while being treated with Ryeqo.

Depression

Carefully observe women with a history of depression and discontinue Ryeqo if depression recurs to a serious degree. Data are limited on the association of Ryeqo 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 in women taking Ryeqo, clinically relevant increases are rare. However, if sustained clinically significant hypertension develops during the use of Ryeqo, hypertension should be treated, and the benefit of continued therapy should be assessed. If treatment with Ryeqo is discontinued, use may be resumed if normotensive values can be 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 Ryeqo, but the evidence of an association with Ryeqo 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.

Lactose

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

4.5. Interaction with other medicinal products and other forms of interaction

Recommendations regarding interactions with Ryeqo 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 of Ryeqo 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:
Co-administration of Ryeqo 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 trials 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 trials 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 of Ryeqo with erythromycin and other oral P-gp inhibitors is not recommended.
azithromycin 500 mg single dose	120 mg single dose**	1.5 -fold ↑	1.6 -fold ↑	If concomitant use with once or twice daily oral P- gp inhibitors is unavoidable (e.g. azithromycin), take Ryeqo 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 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 200 mg QD, multiple doses	40 mg single dose	19% ↑	44% ↑	
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 of Ryeqo with rifampicin and other combined P-gp and strong CYP3A4 inducers is not recommended as the efficacy of the relugolix component of Ryeqo could be reduced.

*Data given as x-fold change represent a ratio between co-administration 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 Ryeqo is not recommended.

Potential for the components of Ryeqo to affect other medicinal products

Relugolix:
Relugolix is a weak inducer of CYP3A4. After co-administration 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 co-administration 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 Ryeqo 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 co-administration 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). Discontinue use of treatment 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 nonclinical 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 discontinuation of Ryeqo.

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

Ryeqo has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

The most frequent adverse drug reactions, in patients being treated for uterine fibroids or endometriosis, were headache (13.2%), hot flush (10.3%) and uterine bleeding (5.8%).
Adverse drug reactions listed in Table 4 are classified according to frequency and system organ class. Within each frequency grouping, adverse drug 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 drug reactions

Table 4. Adverse drug 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
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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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 drug 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, Ryeqo 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 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 treated with Ryeqo 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 > 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 Ryeqo 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 ≤ 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 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 = nonmenstrual pelvic pain; NRS = Numerical Rating Scale, SE = standard error.

Bone mineral density (BMD) measurements over 104 weeks

The effect of Ryeqo 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 treated with Ryeqo 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.

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)	4450 (1980)	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 with Ryeqo 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
Ryeqo must not be used in patients with severe hepatic impairment (see section 4.3). No dose adjustments for Ryeqo 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, sodium starch glycolate, hydroxypropylcellulose, hypromellose 2910, titanium dioxide (E171), magnesium stearate, triacetin, iron oxide yellow (E172)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions. It is recommended to store at room temperature.

6.5. Nature and contents of container

Blister with desiccant packed in foil sachet containing 14 film-coated tablets. Each pack contains 28 or 84 film-coated tablets.

Bottle with desiccant, closed with child-resistant cap containing 28 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

Dexcel Ltd.
1 Dexcel St.
Or Akiva 3060000
Israel

8. MARKETING AUTHORISATION NUMBER

179-33-38165-99

This leaflet format has been determined by the Ministry of Health and the content has been checked and approved in July 2025.