

Factsheet

Relugolix 40mg, Estradiol hemihydrate 1mg and Norethisterone acetate 0.5 milligrams (Ryeqo[®]) tablet ▼
Moderate to severe symptoms of uterine fibroids in adults of reproductive age

Document Control		
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Disclaimer

Factsheets support GPs in taking full and ongoing responsibility for continuing a medicine initiated in secondary care. It differs from a shared care agreement where secondary cares retain a proportion of responsibility for ongoing care.

This document is intended for use by healthcare professionals to aid the treatment of patients within NCL. It should not be used for marketing purposes. If you identify information within this document that is inaccurate, please report to admin.ncl-mon@nhs.net.

Factsheet – Relugolix, estradiol and norethisterone (Ryeqo®) for moderate to severe symptoms of uterine fibroids in adults of reproductive age

Indication information

The NICE technology appraisal (NICE TA832) recommends relugolix–estradiol–norethisterone acetate, within its marketing authorisation, as an option for treating moderate to severe symptoms of uterine fibroids in adults of reproductive age.

As per local formulary agreement, *Ryeqo*® is restricted to the gynaecology consultants. The treatment will be initiated by a hospital consultant and inform the GP on initiation of treatment so that the GP can continue prescribing (typically from 3 months).

The hospital team will:

1. Provide the patient with initial information regarding the treatment and possible adverse effects.
 - a. This includes the risk of arterial or venous thromboembolism (and to report any signs or symptoms to a healthcare professional) and the reduction in menstrual blood loss or amenorrhoea within two months.
 - b. The patient should be advised to report any adverse effects experienced in the first two months to the specialist, and to the GP thereafter.
2. Stop any hormonal contraception prior to starting *Ryeqo*® and inform the patient around appropriate non hormonal contraceptive use in the first month and for a week after two missed doses.
3. Initiate and supply two months supply of *Ryeqo*®. Inform the GP at the point of initiation that *Ryeqo*® has been prescribed (as per NICE TA832)
4. The hospital team will communicate with the GP to request prescribing is continued from month three onwards. Clinically supervise the patient by routine clinic follow-ups initially every 6 months for the first year until a DXA scan is performed. If the DXA scan is normal, the patient can be discharged back to the care of the GP.
5. Patients with risk factors for osteoporosis should have a baseline DXA.
6. Patient should continue indefinitely as long as it is working until the patient reaches the age of natural menopause.

Dose and Administration

Ryeqo® contains 40 mg relugolix (a gonadotropin-releasing hormone-receptor antagonist) combined with 1 mg estradiol (as hemihydrate) and 0.5mg norethisterone acetate mg/day.

The maximum licensed dose is 1 tablet of *Ryeqo*® once daily at approximately the same time each day, with or without food, and continuously.

Starting treatment: 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. Pregnancy must be ruled out prior to initiating treatment with *Ryeqo*®

Renal impairment: No dose adjustment for *Ryeqo*® in patients with mild, moderate, or severe renal impairment is required.

Hepatic impairment: No dose adjustment for *Ryeqo*® in patients with mild or moderate hepatic impairment is required. *Ryeqo*® is contraindicated in women with severe liver disease if liver function values have not returned

to normal.

Discontinuing treatment: Discontinuation should be considered when the patient enters menopause, as uterine fibroids are known to regress when menopause begins. If treatment is discontinued, please contact the gynaecology team and inform the patient that childbearing potential will return rapidly (see information on contraception below). The decision to stop or continue treatment should be clearly communicated to the patient's GP.

Contraception and missed doses: After at least one month of use, Ryeqo® inhibits ovulation and provides adequate contraception. Hormonal contraception needs to be stopped prior to starting Ryeqo®, and nonhormonal methods of contraception should be used in the first month. Childbearing potential will return rapidly after discontinuing treatment.

If a dose is missed, treatment must be taken as soon as possible and then continue the next day at the usual time. If doses are missed for 2 or more consecutive days, a nonhormonal method of contraception is to be used for the next 7 days of treatment.

Counselling: The specialist should inform the patient:

- That they will need nonhormonal contraception for the first month and for a week after two missed doses
- To stop hormonal contraception prior to starting Ryeqo®
- Of the risk of ATE/VTE with Ryeqo®, and to inform a healthcare professional if they experience signs and symptoms of either
- That Ryeqo® usually leads to a reduction in menstrual blood loss or amenorrhoea within the first two months of treatment
- Advise patients to contact their doctor if they experience mood changes and depressive symptoms during treatment. In women with a history of depression please carefully monitor for recurrent depression. GP to discontinue if serious depression.

Adverse Effects

Refer to the SPC and the BNF for full list of side effects.

Adverse effect	Frequency	Suggested management by GP
Irritability	Common	Monitor and if patient cannot tolerate, please consider stopping treatment and refer back to the gynaecology team. Inform patient they will need to use non-hormonal contraception methods if Ryeqo® is stopped.
Hot flush	Common	
Dyspepsia	Common	
Alopecia	Common	
Hyperhidrosis	Common	
Night sweats	Common	
Uterine bleeding including menorrhagia and metrorrhagia	Common	
Decreased libido	Common	
Breast cyst	Common	Stop and refer for a breast scan or to breast team for review. Inform the initiating team and inform patient

		they will need to use non-hormonal contraception methods if Ryeqo® is stopped.
Uterine myoma expulsion	uncommon	Stop treatment and refer back to hospital consultant

Ryeqo® is a black triangle drug and as such is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions using the [Yellow Card | Making medicines and medical devices safer \(mhra.gov.uk\)](https://www.mhra.gov.uk/safer)

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Venous thromboembolic disorder, past or present (e.g. deep vein 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).
- Known osteoporosis
- Headaches with focal neurological symptoms or migraine headaches with aura.
- 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).
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Pregnancy or suspected pregnancy and breastfeeding.
- Genital bleeding of unknown aetiology.
- Concomitant use of hormonal contraceptives.

Special Warnings and Precautions for Use

Any hormonal contraception needs to be stopped prior to initiation of Ryeqo®.

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 oestrogen and a progestogen increases the risk of arterial or venous thromboembolism (ATE or VTE) compared with no use. The specialist will assess the patient for risk factors for ATE or VTE at initiation. The risk of ATE/VTE with Ryeqo® has not been established, and doses of oestrogen and progestogen are lower than that used in combined oral contraceptives.

Table 1 and Table 2 below are taken from the SPC and describe risk factors for ATE and VTE with an oestrogen and progestogen; the risk of ATE/VTE may change over the patients' lifetime whilst on Ryeqo®, so it remains important to be aware of risk factors should the patient report any signs or symptoms of ATE or VTE. If this occurs please discontinue immediately.

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.

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.

Risk of bone loss

In some women treated with Ryego[®], who had normal bone mineral density (BMD) at start of treatment, a bone loss varying from > 3-8% was reported. Therefore, a DXA scan is recommended after the first 52 weeks of treatment. This will be ordered by the specialist and the patient can only be discharged to the care of their GP once a DXA scan demonstrates the patient does not have an unwanted degree of BMD loss that exceeds the benefit of treatment with Ryego[®].

Liver tumours or liver disease

Ryego[®] is contraindicated in women with liver tumours, benign or malignant; or liver disease as long as liver function values have not returned to normal. 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 Ryego[®]. Acute liver test abnormalities may necessitate the discontinuation of Ryego[®] use until the liver tests return to normal.

Renal impairment

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

Change in menstrual bleeding pattern

Ryeqo[®] usually leads to a reduction in menstrual blood loss or amenorrhoea within the first 2 months of treatment. Women receiving Ryeqo[®] 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 assessment 70.6% of women receiving Ryeqo[®] were likely to have amenorrhoea.

Contraceptive properties of Ryeqo[®]

Ryeqo[®] provides adequate contraception when used for at least 1 month. 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 fibroids 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 GP if severe bleeding reoccurs after bleeding symptoms have improved while being treated with Ryeqo[®].

Depression

Data are limited on the association of Ryeqo[®] or other products containing Estradiol and progestins with onset of depression or exacerbation of existing depression. If patients report a recurrence of depression to a serious degree, consider discontinuing Ryeqo[®] and referring back to the specialist.

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 (discuss with the initiating specialist to consider if treatment should be continued; if treatment with Ryeqo[®] is discontinued, use may be resumed if normotensive values can be achieved with antihypertensive treatment).

Laboratory tests

The use of oestrogens 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.

Pregnancy

There is a limited amount of data from the use of relugolix in pregnant women. Ryeqo[®] is contraindicated during pregnancy – 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 oestrogens 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[®].

Breast-feeding

Results from nonclinical studies indicate that relugolix is excreted into the milk of lactating rats. Breastfeeding is contraindicated during the use of Ryeqo[®] and for 2 weeks following discontinuation of Ryeqo[®].

Drug Interactions

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.

Co-administration of Ryeqo[®] with strong CYP3A4 and/or P-gp inducers is not recommended. 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.

The metabolism of oestrogens 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 oestrogens and progestogens.

Herbal preparations containing St John's Wort (*Hypericum perforatum*) may induce the metabolism of oestrogens and progestogens. Clinically, an increase in oestrogen 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.

Oestrogen 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.

'This list is not exhaustive; please consult the BNF or SPC for a full list of potential interactions'

Clinical Monitoring

There is no specific drug monitoring required for Ryeqo[®]. Primary care clinicians should review their patients as per normal practice and be aware of any adverse effects which the patient may report to them (see adverse effects table above).

Prior to the initiation or reinstatement 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 and warnings for use.

Ryeqo® is a black triangle drug and any suspected adverse reactions should be reported using the Yellow Card Scheme. [Yellow Card | Making medicines and medical devices safer \(mhra.gov.uk\)](https://www.mhra.gov.uk/yellowcard)

There is a requirement for a DXA scan to be completed after 12 months of treatment. This will be ordered by the specialist and the decision to stop or continue treatment should be clearly communicated to the patient's GP. If there is no unwanted degree of bone mineral density loss, the patient can be safely discharged to the care of their GP (whilst remaining available for any future queries).

Contact Details

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Women's Health

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References

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2. [BNF](https://bnf.nice.org.uk/drugs/relugolix-with-estradiol-and-norethisterone-acetate/). Available at: <https://bnf.nice.org.uk/drugs/relugolix-with-estradiol-and-norethisterone-acetate/>
3. [NICE TA832: Relugolix–estradiol–norethisterone acetate for treating moderate to severe symptoms of uterine fibroids](https://www.nice.org.uk/guidance/ta832). Available at <https://www.nice.org.uk/guidance/ta832>
4. [Overview | Heavy menstrual bleeding: assessment and management | Guidance | NICE](#)