Relugolix-estradiol-norethisterone (Ryeqo®) and linzagolix (Yselty®)

Information sheet for Primary Care Prescribers

Traffic light classification - Amber 2

Key Points

- Relugolix-estradiol-norethisterone and linzagolix may be prescribed locally for the treatment of moderate to severe symptoms of uterine fibroids and symptomatic treatment of endometriosis in line with NICE TA guidance.
- Treatment will be initiated by a Specialist with a request for Primary Care continuation on a Shared Care basis for at least the first year of treatment (see below). Secondary care will prescribe the first 3 months of treatment.
- For those taking relugolix-estradiol-norethisterone or hormonal ABT alongside linzagolix, there should be a routine annual HRT review. There are no other routine monitoring requirements requested of Primary care. Specialists are responsible for arranging and actioning necessary DXA scans.
- Relugolix-estradiol-norethisterone provides adequate contraception when used *correctly for at least 1 month* but linzagolix has not been demonstrated to provide contraception and effective non-hormonal contraception is required.

Products available

Relugolix-estradiol-norethisterone (Ryeqo®) tablets
containing 40 mg relugolix, 1 mg estradiol and 0.5 mg norethisterone.
cost: £72.00 for 28 tablets

Linzagolix (Yselty®) tablets
containing 100mg and 200mg
cost: £80.00 for 28 tablets

Licensed Indication

Both relugolix- estradiol- norethisterone and linzagolix are licensed for use in adult women of reproductive age for the treatment of moderate to severe symptoms of uterine fibroids and symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis.

Therapeutic summary

Relugolix and linzagolix are GnRH receptor antagonists that block the pituitary gland from releasing LH and FSH, thereby decreasing progesterone and oestrogen production. As suppressing oestrogen levels also induces symptoms of menopause, hormonal add back therapy (ABT) is usually given to reduce these and any associated loss of BMD.

Relugolix-norethisterone-estradiol is fixed dose combination tablet that contains the ABT as oral HRT. Linzagolix is taken separately to the ABT so offers an option for those in whom oral HRT is unsuitable or unwanted; it's availability as a lower dose allows the possibility of using without ABT if desired for the treatment of fibroids.

Uterine Fibroids
Initial treatment options for symptoms of uterine fibroids include levonorgestrel-releasing intrauterine system or combined hormonal contraception. For treating moderate to severe symptoms of uterine fibroids, injectable gonadotrophin-releasing hormone (GnRH) agonists e.g. triptorelin may be used. Relugolix-estradiol-norethisterone (Ryeqo®) and linzagolix are alternative oral treatment options for moderate to severe symptoms of uterine fibroids recommended by NICE in TA832 and TA996. All common pharmacological methods to control fibroid-related heavy periods should have been considered before either relugolix-estradiol-norethisterone or linzagolix are considered.

Endometriosis
Treatments for endometriosis aim to manage its symptoms but do not resolve the underlying condition. Current treatments aim to improve quality of life and maximise fertility for people for whom this is important. After pain relief and hormonal treatments, options include surgery or GnRH agonists e.g. triptorelin. Relugolix–estradiol–norethisterone and linzagolix are alternative oral treatment options recommended by NICE in TA1057 and TA1067.

Medicines Initiation
Treatment will be initiated by the Specialist, and the first 3-months of treatment will be prescribed from Secondary care followed on by supply by Primary care on a shared care basis for at least the first year of treatment as detailed below.

Pregnancy must be ruled out prior to initiating or re-initiating treatment. Advice should be provided at initiation about contraception requirements (see Patient information) and a management plan made for if a patient wishes to attempt pregnancy. Specialists will be responsible for assessing for contraindications and precautions prior to treatment initiation.

At 6 months: Patients will be reviewed by the Specialist after 6 months where a plan will be made for longer term management and this will be communicated to the patient and Primary care.

At 1 year: The specialist will request a DXA scan for after 1 year of treatment and action the results. If the scan results are satisfactory and the patient is taking Ryeqo® or linzagolix with hormonal add-back therapy (ABT), the specialist may then request the patient's GP to take over full prescribing responsibilities of treatment.

Ongoing: Patients taking linzagolix without hormonal ABT require an annual DXA scan and other patients may require ongoing DXA scans depending on individual risk and previous BMD assessment. The frequency of these will be determined by the Specialist. **These patients should remain under the care of the Specialist.**

Dosages and route of administration

Relugolix-estradiol-norethisterone
*Uterine fibroids & Endometriosis**:***
- One tablet orally 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.

Linzagolix:
Uterine fibroids:
- with hormonal add-back therapy (ABT*): 200 mg orally once daily
- without hormonal ABT: 200 mg once daily for 6 months, then 100 mg once daily
- When starting treatment, it should preferably be started in the first week of the menstrual cycle.
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Endometriosis:
- 200 mg orally once daily with hormonal add-back therapy (ABT*)
- When starting treatment, it should preferably be started in the first week of the menstrual cycle

* The hormonal ABT recommended in the SPC is estradiol 0.5mg and norethisterone 1mg tablet orally once daily.

Duration of treatment and deprescribing guidance

Relugolix-estradiol-norethisterone and linzagolix can be taken without interruption for as long as treatment is effective. Discontinuation should be attempted at menopause/ age 51 years as the symptoms of endometriosis and uterine fibroids are known to regress once the patient enters menopause. When discontinuing relugolix-estradiol-norethisterone alternative contraception needs to be started immediately after discontinuation of treatment.

Treatment should also be discontinued if the patient wishes to attempt pregnancy.

Monitoring Requirements and Responsibilities

There are no routine monitoring requirements requested of Primary Care for the relugolix constituent or linzagolix. For patients taking relugolix-estradiol-norethisterone or hormonal ABT alongside linzagolix:

- a routine annual HRT review should be conducted by Primary Care, including assessment of blood pressure.

If linzagolix is used in those with pre-existing Chronic Kidney Disease, liver abnormalities or elevated lipids, ongoing monitoring is advised in line with routine management of these conditions (see precautions).

Dual X ray absorptiometry (DXA/ DEXA) scans are recommended as follows:
It is the Specialist's responsibility to arrange and action the results of the DXA scan.

- At baseline (if indicated)
- At 1 year- all patients
- Regular annual scan- only for patients taking linzagolix without hormonal ABT
- Repeat scan- as clinically indicated (depending on individual risk and previous BMD assessment)

Management of Adverse effects and criteria for review

Adverse Effect	*Management advice*
Irritability, hot flush, nausea, dyspepsia, alopecia, hyperhidrosis, night sweats, decreased libido, athralgia.	Monitor; if patient cannot tolerate, consider stopping treatment and refer back to the gynaecology team.
Symptoms of VTE (deep vein thrombosis and pulmonary embolism)	Discontinue treatment (including hormonal ABT if taken with linzagolix) and refer for urgent medical attention. If confirmed refer to specialist for ongoing management of uterine fibroids/ endometriosis.
Symptoms of ATE (Cerebrovascular accident, Transient ischaemic attack, Myocardial infarction)	
Liver test abnormalities (e.g. LFTs 3xULN)	Discuss with specialist; discontinuation may be required until the liver tests return to normal.
Renal impairment whilst taking *linzagolix* (no dosage adjustment required for Ryeqo in renal impairment)	Discuss with specialist if eGFR is persistently below 60 ml/min. Patients should be monitored for adverse reactions if there is mild renal impairment (eGFR = 60-89 mL/min)
Clinically significant hypertension	Treat hypertension; the benefit of continued therapy should be assessed. Treatment may be continued if normotensive values can be achieved with antihypertensive treatment.
Increased QT interval whilst taking *linzagolix*	See precautions, discuss with specialist
Persistent excessive vaginal bleeding or severe bleeding reoccurs after bleeding symptoms have improved	Refer to specialist
Mood changes and depressive symptoms	Discuss with specialist; consideration should be given to discontinuation if severe depressive symptoms
Uterine myoma expulsion	Discontinue treatment and refer to specialist
Missed doses	**Relugolix-estradiol-norethisterone:** 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 **Linzagolix:** If a dose is missed, treatment must be taken as soon as possible and then continued the next day at the usual time.
Pregnancy	Discontinue treatment and seek Specialist advice

Whilst relugolix-estradiol-norethisterone and linzagolix are subject to Black triangle status▼, Health Care Professionals are asked to report any suspected adverse reactions to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard.

For information on incidence of ADRs see relevant summaries of product characteristics

Contraindications:

- Hypersensitivity to the active substance(s) or to any of the excipients listed in the SPC
- Pregnancy or breast-feeding
- Known osteoporosis
- Genital bleeding of unknown aetiology
- Concomitant use of hormonal contraceptives
- Linzagolix should be avoided in women with moderate (eGFR = 30-59 mL/min), severe (eGFR < 30 mL/min) renal impairment or end-stage renal disease.
- Severe liver disease if liver function values have not returned to normal.
- Contraindications related to hormonal ABT should be respected if concomitant ABT is given with linzagolix. Additional contraindications exist for relugolix-estradiol-norethisterone related to the hormonal component including:
    - 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).
    - 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).

Precautions:

- **Thromboembolism**. The use of medicinal products containing an estrogen and a progestogen increases the risk of arterial or venous thromboembolism (ATE or VTE). The risk may increase substantially in a woman with additional risk factors e.g. obesity, positive family history in a sibling or parent especially at a relatively early age e.g. before 50 years, increasing age, other medical conditions associated with VTE or ATE. And specifically, for VTE; prolonged immobilisation, major surgery or major trauma and for ATE; smoking, hypertension and migraine.
- **Depression.** Monitor carefully for mood changes/ depressive symptoms
- **Hypertension.** Ryeqo/ linzagolix treatment may be continued if normotensive values are achieved with antihypertensive treatment.
- **Gallbladder** disease.
- **Low BMD**. History of a low trauma fracture or other risk factors for osteoporosis or bone loss (e.g. chronic alcohol and/or tobacco use, strong family history of osteoporosis, and low body weight, those taking medications that may affect BMD (e.g., systemic corticosteroids, anticonvulsants))
    - a DXA scan should be conducted prior to treatment in these patients

Linzagolix only (additional precautions to above):

- **QT prolongation.** Linzagolix marginally increases the QT interval; caution should be exercised in patients who have known cardiovascular disease, family history of QT prolongation or hypokalaemia, in concomitant use with medicinal products known to prolong the QT interval and in those with co-existing disorders leading to increased linzagolix plasma levels (e.g. renal impairment).
- **Renal impairment.** Linzagolix levels may be increased in renal impairment. Those with mild renal impairment (eGFR = 60-89 mL/min) should be monitored for adverse reactions. Linzagolix should not be used in those with more severe renal impairment (see above)
- **Liver impairment.** Linzagolix has been associated with asymptomatic transient liver enzyme elevations. For patients with known abnormal hepatic history should be treated with caution and
  - a baseline level of hepatic function tests should be obtained, and
  - further regular monitoring should be performed.
- **Elevated lipids.** For patients who are taking linzagolix with pre-existing elevated lipid profiles monitoring of lipid levels is recommended.

Clinically relevant medicine interactions and their management

Relugolix-estradiol-norethisterone:

- **Oral P-gp inhibitors**- e.g. some antibiotics (erythromycin, clarithromycin, gentamicin, tetracycline), anti-fungals (ketoconazole, itraconazole), antihypertensives (e.g. carvedilol, verapamil), antiarrhythmics (e.g. amiodarone, dronedarone, propafenone, quinidine), ranolazine, cyclosporine, protease inhibitors (e.g. ritonavir, telaprevir). **Increased exposure to relugolix, not recommended.** If concomitant use is unavoidable take relugolix-norethisterone-estradiol first, and separate dosing with the P-gp inhibitor by at least 6 hours; monitor patients more frequently for adverse reactions.
- **Strong CYP3A4 and/or P-gp inducers** e.g. anticonvulsants (e.g. carbamazepine, topiramate, phenytoin, phenobarbital, primidone, oxcarbazepine, felbamate), anti-infectives (e.g. rifampicin, rifabutin, griseofulvin); St. John's wort (Hypericum perforatum); bosentan, protease inhibitors (e.g. ritonavir, boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz). **Not recommended - decreased levels of both relugolix and the hormonal ABT.**
- **CYP3A4 inhibitors**- increased exposure to estrogen and norethisterone.
- **Estrogen and progestogen** 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 relugolix- estradiol-norethisterone. Dose adjustment of these medicinal products may be necessary.

Linzagolix:

- Avoid concomitant use with medicinal products with a narrow therapeutic index primarily cleared by CYP2C8 metabolism e.g. paclitaxel, sorafenib and repaglinide- increased exposure.

Information given to patient

Uterine fibroids:	Women's Health Concern British Fibroid Trust Fibroids - Treatment - NHS
Endometriosis:	Information | Endometriosis UK Endometriosis - NHS Endometriosis | RCOG

Patient information leaflets on relugolix-estradiol-norethisterone and linzagolix are also available from Home - electronic medicines compendium (emc).

The patient must be advised:

- To **seek urgent medical attention** (promptly, without delay) for any of the following signs or symptoms:
  - symptoms of **VTE or ATE**
  - symptoms or signs that may reflect **liver injury**, such as **jaundice**
- **Pregnancy avoidance.** Treatment with relugolix-estradiol-norethisterone or linzagolix usually leads to a significant reduction in menstrual blood loss and often leads to amenorrhoea, which may reduce the ability to recognise the occurrence of a pregnancy in a timely manner. Pregnancy testing should be performed if pregnancy is suspected. If pregnancy is confirmed, treatment should be discontinued and medical advice sought.
- **Contraception.**
  - Relugolix-estradiol-norethisterone provides adequate contraception when used correctly for at least 1 month. However, ovulation will return rapidly after discontinuing treatment. Therefore, alternative contraception needs to be started immediately after discontinuation of treatment. 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.
  - Linzagolix with or without concomitant ABT has not been demonstrated to provide contraception. Women of childbearing potential at risk of pregnancy must use effective non-hormonal contraception while on treatment.
- **Fibroids**. Women known or suspected to have submucosal uterine fibroids should be advised regarding the possibility of uterine fibroid prolapse or expulsion during treatment and should contact their physician if severe bleeding reoccurs after bleeding symptoms have improved.
- **Mood changes**. Women must be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

References

Ryeqo® Summary of Product Characteristics. Last updated on www.medicines.org.uk 09/09/2024.
Yselty® Summary of Product Characteristics. Last updated on www.medicines.org.uk 08/05/2025.
NICE guideline NG73: Endometriosis: diagnosis and management, last updated November 2024.
NICE TA1067: linzagolix with hormonal add-back therapy for endometriosis, June 2025
NICE TA1057: relugolix–estradiol–norethisterone for endometriosis, April 2025.
NICE NG88: Heavy menstrual bleeding: assessment and management. Last updated May 2021
NICE TA832: Relugolix–estradiol–norethisterone acetate for treating moderate to severe symptoms of uterine fibroids, October 2022
NICE TA996: Linzagolix for treating moderate to severe symptoms of uterine fibroids, August 2024

Accessibility checked. Contains tables which may not be accessible to screen readers.