RELUGOLIX-ESTRADIOL-NORETHISTERONE ACETATE tablets (Ryeqo® ▼) for treating symptoms of endometriosis

Bath and North East Somerset, Swindon and Wiltshire Together

The BSW Area Prescribing Committee recommends the prescribing of RELUGOLIX-ESTRADIOL-NORETHISTERONE ACETATE tablets (Ryeqo® ▼) for treating symptoms of endometriosis in accordance with NICE TA1057.

AMBER following specialist initiation: 1-month supply

NICE recommendation for use (NICE TA1057)[1]

NICE technology appraisal TA1057 (16th April 2025) recommends relugolix-estradiol-norethisterone acetate as **an option for treating symptoms of endometriosis in adults of reproductive age who have had medical or surgical treatment for endometriosis.**

After pain relief and hormonal treatment, usual treatment options for endometriosis are gonadotropin-releasing hormone (GnRH) agonists and surgery. There is no cure for endometriosis, and there is an unmet need for long-term and non-invasive (non-surgical and not injected) treatments for its symptoms.

Costing information[2]

The NHS list price (excluding VAT) of relugolix-estradiol-norethisterone acetate is £72.00 for a 28-pack and £216.00 for an 84-pack (July 25). The annual treatment cost per patient is £939.00.

Clinical Effectiveness[1,3]

Clinical trial evidence shows that relugolix-estradiol-norethisterone acetate reduces pain compared with placebo. Relugolix-estradiol-norethisterone acetate has not been directly compared in a clinical trial with usual treatment. Indirect comparisons suggest that it is likely to reduce pelvic pain almost as well as GnRH agonists. But it is unclear how well relugolix-estradiol-norethisterone acetate works compared with surgery.

Relugolix-estradiol-norethisterone acetate 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, relugolix-estradiol-norethisterone acetate provides adequate contraception when taken for at least 1 month.

Adverse effects/contra-indications[2,3] See SPC for full safety data, cautions and interactions.

Contraindications include hypersensitivity to the active substances or to any of the excipients, past or present venous thromboembolic disorder, past or present arterial thromboembolic cardiovascular disease, known thrombophilic disorders, 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, presence or history of severe hepatic disease as long as liver function values have not returned to normal, pregnancy or suspected pregnancy, breastfeeding, genital bleeding of unknown aetiology, and concomitant use of hormonal contraceptives.

The most frequent adverse drug reactions in clinical trials were hot flush (8.3%) and uterine bleeding (4.7%). Bone loss (varying from 3-8%) has been reported in patients who had normal bone mineral density (BMD) at the start of treatment.

The use of medicinal products containing estrogen and progestogen increases the risk of arterial or venous thromboembolism (ATE or VTE) compared with no use. The risk of ATE/VTE with relugolix-estradiol-norethisterone acetate has not been established.

Patient factors[2,3]

Patients with a history of depression should be carefully monitored.

No dose adjustment is required for patients with mild, moderate, or severe renal impairment.

No dose adjustment required for patients with mild or moderate hepatic impairment, but relugolix-estradiol-norethisterone acetate is contraindicated in patients with severe liver disease if liver function values have not returned to normal.

Prescribing information[2,3]

- Treatment should only be initiated by a specialist in the management of endometriosis. **After a minimum of one month's treatment, the specialist may ask the patient's GP to take over prescribing responsibilities of treatment. The patient will be followed up by secondary care (usually at months 4,8 and 12 although this will be determined**

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on an individual patient basis) then annually. This may be in-person or remotely.

- Prior to initiation or reinstitution, a complete medical history (including family history) will be taken by the specialist. Blood pressure and a physical examination must be performed guided by the contraindications and warnings for use.
- The SPC states that 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 dual X ray absorptiometry (DXA) scan is recommended prior to starting treatment (see monitoring section below). Treatment should not be initiated if the risk associated with BMD loss exceeds the potential benefit of the treatment.
- Relugolix-estradiol-norethisterone acetate can be taken without interruption. Discontinuation should be considered when the patient enters menopause, as the symptoms of endometriosis are known to regress at that point.
- Do not use HRT with relugolix-estradiol-norethisterone acetate.
- **Contraceptive properties of Relugolix-estradiol-norethisterone acetate**: Any hormonal contraception needs to be stopped prior to initiation of treatment, as concomitant use of hormonal contraceptives is contraindicated.
- Nonhormonal methods of contraception must be used for at least 1 month after initiation of treatment.
- After at least one month of continuous use, relugolix-estradiol-norethisterone acetate 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. A discussion with the patient, regarding appropriate contraceptive methods, must take place prior to discontinuing treatment and alternative contraception must be started immediately after discontinuation of treatment.
- 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.

Monitoring[2,3]

- For 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 specialist.
- A DXA scan is recommended in the SPC prior to starting treatment in patients with risk factors for osteoporosis or bone loss and/or after the first year of treatment. However, following discussions with local gynaecology and osteoporosis teams, a baseline or 1-year DXA scan is not felt to be necessary for the majority of patients taking Relugolix-estradiol-norethisterone acetate unless they have significant other risk factors for impaired bone health (for example, current use of oral or systemic glucocorticoids, or previous fragility fracture).
- Patients must be counselled on symptoms of ATE and VTE by the specialist. In the event of symptoms of ATE or VTE, patients must be advised to seek urgent medical attention and to inform the physician that they are taking relugolix-estradiol-norethisterone acetate. If arterial thromboembolism (ATE) or Venous thromboembolism (VTE) occurs, treatment must be stopped immediately. The risk for venous thromboembolic complications may increase substantially in a patient with additional risk factors, see SPC for further information regarding risk factors for ATE and VTE.
- Patients with a history of depression should be carefully monitored and advised to seek medical attention in case of mood changes and depressive symptoms, including shortly after initiating the treatment. The benefit of continued therapy should be assessed by the consultant in Gynaecology who started the medication, but treatment should be stopped if depression recurs to a serious degree.
- If sustained clinically significant hypertension develops during treatment, it should be treated, and the benefit of continued therapy should be assessed by the consultant gynaecologist who started the relugolix-estradiol-norethisterone acetate. If treatment is discontinued**,** use may be resumed if normotensive values can be achieved with antihypertensive treatment.

References

1. National Institute for Health and Care Excellence. Technology appraisal 1057; Relugolix-estradiol-norethisterone acetate –estradiol–norethisterone for treating symptoms of endometriosis 16th April 2025
2. British National Formulary (BNF) March 2023 Relugolix-estradiol-norethisterone acetate with estradiol and norethisterone acetate | Drugs | BNF | NICE
3. Gedeon Richter (UK) Ltd. Summary of Product Characteristics; Ryeqo 40mg/1mg/0.5mg film-coated tablets, 08/05/2025.