RELUGOLIX-ESTRADIOL-NORETHISTERONE ACETATE tablets (Ryeqo® ▼) for treatment of uterine fibroids

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 uterine fibroids in accordance with NICE TA832.

AMBER following specialist initiation: 1-month supply

NICE recommendation for use (NICE TA832)[1]

NICE technology appraisal TA832 (19 October 2022) recommends relugolix-estradiol-norethisterone acetate as an option for treating moderate to severe symptoms of uterine fibroids in adults of reproductive age.

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 are often used before surgical options. Relugolix- estradiol-norethisterone acetate (Ryeqo®), taken orally, is another treatment option for moderate to severe symptoms of uterine fibroids. All common pharmacological methods to control fibroid-related heavy periods should have been considered before Ryeqo®. Local specialists consider Ryeqo® positioning to follow commonly used pharmacological control of bleeding and before surgical options e.g. fibroid resection, ablations, myomectomy or hysterectomy.

Costing information[2]

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

Clinical Effectiveness[1,3]

Relugolix is a non-peptide GnRH receptor antagonist that suppresses ovarian production of estrogen and progesterone. When administered exogenously, estradiol alleviates symptoms associated with a hypoestrogenic state, such as vasomotor symptoms and bone mineral density loss. Norethisterone acetate is a synthetic progestogen which reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women. The clinical evidence for relugolix-estradiol-norethisterone acetate is from two identical phase 3 randomised controlled trials LIBERTY 1 & LIBERTY 2. NICE concluded that the results from LIBERTY 1 & 2 showed that relugolix- estradiol-norethisterone acetate is more effective than placebo for treating heavy menstrual bleeding associated with uterine fibroids.

Adverse effects/contra-indications[2,3]

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 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 relugolix-estradiol- norethisterone acetate has not been established. See SPC for full safety data, cautions and interactions.

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 Ryeqo® is contraindicated in patients with severe liver disease if liver function values have not returned to normal.

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Prescribing information[2,3]

- Treatment should only be initiated by a specialist in the management of uterine fibroids. **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 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.
- In patients with risk factors for osteoporosis or bone loss, a dual X-ray absorptiometry (DXA) 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.
- Ryeqo® can be taken without interruption. Discontinuation should be considered when the patient enters menopause, as uterine fibroids are known to regress when menopause begins.
- Do not use HRT with Ryeqo®
- **Contraceptive properties of Ryeqo®:** Any hormonal contraception needs to be stopped prior to initiation of Ryeqo® 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, 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. 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.

Monitoring[2,3]

- Ryeqo® can be expected to lead to a reduction in menstrual bleeding or amenorrhoea within 1-2 months of treatment. If bleeding is not controlled within ~6 months, treatment will be discontinued by the specialist. In case of persistent excessive bleeding, patients must notify their specialist.
- A DXA scan is recommended in the SPC prior to starting treatment with Ryeqo® 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 Ryeqo® 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 Ryeqo®. If ATE or 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 specialist but treatment should be stopped if depression recurs to a serious degree.
- If sustained clinically significant hypertension develops during treatment with Ryeqo®, hypertension should be treated and the benefit of continued therapy should be assessed by the specialist. 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 832; Relugolix–estradiol–norethisterone acetate for treating moderate to severe symptoms of uterine fibroids, 19 October 2022
2. British National Formulary (BNF) March 2023 Relugolix 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, 12 September 2022.

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