NHS
Pan Mersey
Area Prescribing Committee

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

The Pan Mersey 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

NICE technology appraisal (TA) 832 (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.[1]

Treatment options for symptoms of uterine fibroids include levonorgestrel-releasing intrauterine system or combined hormonal contraception. However, 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, taken orally, is another treatment option for moderate to severe symptoms of uterine fibroids.[1]

Costing information

NICE does not expect this guidance to have a significant impact on resources; that is, the resource impact of implementing the recommendations in England will be less than £5 million per year (or approximately £9,000 per 100,000 population). This is because relugolix-estradiol-norethisterone acetate is a further treatment option and is available at a similar price to the current treatment options.[2]

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

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Effectiveness

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.[3]

The clinical evidence for relugolix-estradiol-norethisterone acetate is from 2 identical phase 3 randomised controlled trials, LIBERTY 1 and LIBERTY 2. The trials compared relugolix-estradiol-norethisterone acetate (n=128 and n=126 respectively), relugolix with delayed estradiol and norethisterone acetate (n=132 and n=127 respectively) and placebo (n=128 and n=129 respectively) for heavy menstrual bleeding associated with uterine fibroids. The key inclusion criteria in the trials were premenopausal state, age 18 to 50 years, regular menstrual periods lasting less than 14 days, a cycle of 21 to 38 days, a diagnosis of fibroids confirmed with ultrasonography, and heavy menstrual bleeding. Planned surgery within 6 months of enrolment was an exclusion criterion in both trials. None of the data from the relugolix with delayed estradiol and norethisterone acetate arms from the trials were considered by NICE. The primary outcome measure was a menstrual blood loss volume of less than 80 ml and at least a 50% reduction from baseline in menstrual blood loss volume over the previous 35 days of treatment. The results from the LIBERTY 1 and 2 showed that the primary outcome measure was reached by 73% and 71% respectively of people in the relugolix-estradiol-norethisterone acetate compared with 19% and 15% respectively in the placebo arms. NICE concluded that the results from LIBERTY 1 and 2 showed that relugolix-estradiol-norethisterone acetate is more effective than placebo for treating heavy menstrual bleeding associated with uterine fibroids.[1]

Safety[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.

Refer to SPC for full safety data, cautions and interactions.

Cost

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.[4] The annual treatment cost per patient is £939.00.

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Patient factors[3]

Contraindicated in pregnancy, suspected pregnancy, and breastfeeding. 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 is 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[3]

- Each film-coated tablet contains 40 mg relugolix, 1 mg estradiol, and 0.5 mg norethisterone acetate.
- One tablet of relugolix-estradiol-norethisterone acetate must be taken once daily, at about the same time with or without food. Tablets should be taken with some liquid as needed.
- Any hormonal contraception needs to be stopped prior to initiation. Non-hormonal methods of contraception must be used for at least 1 month after initiation of 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 non-hormonal method of contraception is to be used for the next 7 days of treatment.
- Pregnancy must be ruled out prior to initiating or re-initiating 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.
- The change in menstrual bleeding pattern may reduce the ability to recognise the occurrence of a pregnancy. Perform pregnancy testing if pregnancy is suspected and discontinue treatment if pregnancy is confirmed.
- Relugolix-estradiol-norethisterone acetate can be taken without interruption.
- Discontinuation should be considered when the patient enters menopause, as uterine fibroids are known to regress when menopause begins.

Implementation notes

- Treatment should only be initiated by a specialist in the management of uterine fibroids. Prescribing is to be continued by the specialist until stabilisation of the patient's condition is achieved, and the patient has been reviewed by the specialist. The specialist may then request the patient's GP to take over prescribing responsibilities of treatment.
- The patient should remain under the care of the specialist (ie not discharged) for the first year of treatment and until the results of the DXA scan have been actioned. The decision to stop or continue treatment should be clearly communicated to the patient's GP.
- Prior to initiation or reinstitution, 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. During treatment, periodic check-ups must be carried out according to standard clinical practice.[3]
- In patients with risk factors for osteoporosis or bone loss, a dual X-ray absorptiometry (DXA) is recommended prior to starting treatment. Treatment should not be initiated if the risk associated with BMD loss exceeds the potential benefit of the treatment. [3]

Monitoring

- A DXA scan is recommended after the first year of treatment.[3] It would be the responsibility of the specialist to request the scan and to action the results. The decision to stop or continue treatment should be clearly communicated to the patient's GP.
- 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.[3]
- If ATE or VTE occurs, treatment must be discontinued immediately. The risk for venous thromboembolic complications may increase substantially in a patient with additional risk factors. Refer to SPC for further information regarding risk factors for ATE and VTE.[3]
- Patients should be informed by the specialist that treatment usually leads to a reduction in menstrual blood loss or amenorrhoea within the first 2 months of treatment. In case of persistent excessive bleeding, patients must notify their specialist.[3]
- Patients with a history of depression should be carefully monitored and must be 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. However, treatment should be discontinued if depression recurs to a serious degree.[3]

- If sustained clinically significant hypertension develops during treatment with relugolix-estradiol-norethisterone acetate, 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.[3]

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. Accessed online 02 November 2022.
2. National Institute for Health and Care Excellence. Technology appraisal 832; Relugolix–estradiol–norethisterone acetate for treating moderate to severe symptoms of uterine fibroids Resource impact statement, 19 October 2022. Accessed online 02 November 2022.
3. Gedeon Richter (UK) Ltd. Summary of Product Characteristics; Ryeqo 40mg/1mg/0.5mg film-coated tablets, 28 July 2022. Accessed 15 November 2022.
4. NHS Business Services Authority. Dictionary of medicines and devices (dm+d) browser. Accessed 07 June 2022.