Therapeutics Advisory Group

Improving lives together
Norfolk and Waveney Integrated Care System

Commissioning Statement for

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

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Norfolk and Waveney TAG recommends the prescribing of RELUGOLIX-ESTRADIOL-NORETHISTERONE ACETATE tablets (Ryeqo®▼) for treating uterine fibroids in accordance with NICE TA832.

ADVICE - SPECIALIST INITIATION: First three months supplied by specialist

NICE recommendation TA 832[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, confirmed by ultrasonography, 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® as agreed by local specialists.
- Surgical options e.g. fibroid resection, ablations, myomectomy or hysterectomy.

Clinical Effectiveness[1,2,3]

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 / Contraindications[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 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.

Patient Considerations[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.
- mild or moderate hepatic impairment, but Ryeqo® 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 uterine fibroids. After a minimum of three 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. 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®: Hormonal contraception needs to be stopped prior to initiation of Ryeqo®, as concomitant use of hormonal contraceptives is contraindicated.
- Nonhormonal 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]

- A reduction in menstrual bleeding or amenorrhoea can be expected within 1-2 months of treatment. If bleeding is not controlled within ~6 months, treatment will be discontinued by the specialist. Patients must notify their specialist of persistent excessive bleeding.
- DXA scan - 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 and 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. see SPC
- 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. TA 832;** Overview | Relugolix–estradiol–norethisterone acetate for treating moderate to severe symptoms of uterine fibroids | Guidance | NICE
2. **British national Formulary (BNF) May 2023** Relugolix with estradiol and norethisterone acetate | Drugs | BNF | NICE
3. **Summary of Product Characteristics Ryeqo** Ryeqo 40mg/1mg/0.5mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) **May 2023**

Title	Commissioning Statement for RELUGOLIX-ESTRADIOL-NORETHISTERONE ACETATE tablets (Ryeqo®▼) for treatment of uterine fibroids
Description of policy	*To inform healthcare professionals*
Scope	*Norfolk and Waveney Integrated Care System*
Prepared by	Norfolk and Waveney ICB Medicines Optimisation Team
Impact Assessment (Equalities and Environmental)	*Please indicate impact assessment outcome:* *Positive impact* *Adverse impact - low - action plan completed as per guidance* *Adverse impact - medium - action plan completed as per guidance*

	Adverse impact - high - action plan completed as per guidance *No impact* ***No policy will be approved without a completed equality impact assessment***
Other relevant approved documents	
Evidence base / Legislation	Level of Evidence: *A. based on national research-based evidence and is considered best evidence* ***B. mix of national and local consensus*** *C. based on local good practice and consensus in the absence of national research based information.*
Dissemination	Is there any reason why any part of this document should not be available on the public web site? ☐ Yes / No ☒
Approved by	*Norfolk & Waveney Therapeutics Advisory Group (TAG) (Date)*
Authorised by	*Norfolk & Waveney Drug Integrated Care Board on behalf of the ICS (Date)*
Review date and by whom	Medicines Optimisation Team
Date of issue	Oct 2023

Version Number	Author	Purpose / Change	Date
1.0	M. Sully	To support prescribing	Oct 2023