

## Relugolix–Estradiol–Norethisterone Prescribing Support Information

This information is provided to support primary care clinicians prescribing relugolix–estradiol–norethisterone (Ryeqo®) in Bedfordshire, Luton and Milton Keynes.

<b>Category</b>	Relugolix is a non-peptide gonadotrophin-releasing hormone (GnRH) receptor antagonist that prevents follicular growth and development, thereby reducing production of oestrogen and progesterone. Relugolix is combined with the oestrogen estradiol to reduce symptoms related to lowered levels of oestrogen, and the progestogen norethisterone to counteract estradiol-induced endometrial hyperplasia.
<b>Therapeutic indications</b>	<ul style="list-style-type: none"> <li>• Treatment of moderate to severe symptoms of uterine fibroids.</li> <li>• Symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis.</li> </ul>
<b>Pharmaceutical form</b>	Ryeqo® 40 mg/1 mg/0.5 mg film-coated tablets are a combination of 40 mg relugolix, 1 mg estradiol (as hemihydrate), and 0.5 mg norethisterone acetate.
<b>NICE guidance</b>	<ul style="list-style-type: none"> <li>• Relugolix–estradiol–norethisterone acetate is recommended, within its marketing authorisation, as an option for treating moderate to severe symptoms of uterine fibroids in adults of reproductive age (<a href="#">NICE TA832</a>, published 19 October 2022).</li> <li>• Relugolix–estradiol–norethisterone (relugolix combination therapy [CT]) can be used, within its marketing authorisation, as an option for treating symptoms of endometriosis in adults of reproductive age who have had medical or surgical treatment for endometriosis (<a href="#">NICE TA1057</a>, published 16 April 2025).</li> </ul>
<b>Formulary status</b>	<b>SpIS</b> specialist initiation and stabilisation (specialist to initiate treatment and prescribe for the initial three months, to ensure tolerability and response, prior to continuation in primary care).
<b>Specialist Responsibilities</b>	<ul style="list-style-type: none"> <li>• Assessment of complete medical history (including family history and ruling out pregnancy) and medication history.</li> <li>• Blood pressure measurement, pre-treatment LFTs, and physical examination.</li> <li>• Arrange <a href="#">DXA scan</a> prior to commencing treatment, if indicated, and DXA scan at 52 weeks for all patients.</li> <li>• Provide the patient with initial information/counselling regarding the treatment and possible adverse effects.</li> <li>• Advise patients to contact their doctor if they experience mood changes and depressive symptoms during treatment.</li> <li>• Advise patients of childbearing potential that ovulation and menstrual bleeding will return rapidly after discontinuing treatment.</li> <li>• Discuss appropriate contraceptive methods, prior to discontinuing treatment, and advise the patient that alternative contraception needs to be started immediately after discontinuation of treatment.</li> </ul>
<b>Primary Care Responsibilities</b>	<ul style="list-style-type: none"> <li>• Annual blood pressure check and medication review (to encompass tolerability / consideration of adverse effects, and potential drug interactions).</li> <li>• Monitor for relevant changes in patient history, such as migraines with aura or unprovoked VTE in a family member. See also <a href="#">cautions</a> and <a href="#">contraindications</a>.</li> </ul>

This information does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it. Please see [BNF](#) & [SPC](#) for comprehensive information.

**The following organisations contribute to and participate in the BLMK APC – Bedfordshire, Luton and Milton Keynes Integrated Care Board; Bedfordshire Hospitals NHS Foundation Trust; Cambridgeshire Community Services NHS Trust; Central and North West London NHS Foundation Trust; East London NHS Foundation Trust; Milton Keynes University Hospital NHS Foundation Trust**

	<ul style="list-style-type: none"> <li>Monitor the efficacy of Ryeqo® in managing fibroid / endometriosis symptoms and need for ongoing therapy.</li> </ul> <p>Note: an acceptable response will be demonstrated by reduction in fibroid size, reduction of heavy menstrual bleeding and/or dysmenorrhoea, and improvement in quality of life.</p>
<b>Dosing Advice</b>	<p>One 40mg/1mg/0.5mg tablet daily, at about the same time with or without food.</p> <p>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.</p>
<b>Missed doses</b>	<p>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.</p> <p>If two or more tablets are missed for consecutive days, contraceptive protection may be reduced. A non-hormonal method of contraception is to be used for the next 7 days of treatment.</p>
<b>Stopping treatment</b>	<p>Ryeqo® can be taken without interruption. Discontinuation should be considered when the patient enters menopause, as the symptoms of both uterine fibroids and endometriosis are known to regress when menopause begins. Take into account symptoms and family history for age of menopause when considering stopping treatment, taking a similar approach to the review of progesterone only contraception in the perimenopause. Treatment can be recommenced if symptoms recur.</p> <p>Treatment should be discontinued if the patient develops jaundice, any <a href="#">contraindications</a>, if severe depression recurs, pregnancy; if sustained clinically significant hypertension develops during the use of Ryeqo®, hypertension should be treated, and the benefit of continued therapy should be assessed. If treatment with Ryeqo® is discontinued, use may be resumed if normotensive values can be achieved with antihypertensive treatment.</p>
<b>Special patient populations</b>	<p><b>Renal impairment:</b> No dose adjustment is required in patients with renal impairment.</p> <p><b>Hepatic impairment:</b> No dose adjustment is required in patients with mild or moderate hepatic impairment. Use is contraindicated in women with severe liver disease if liver function values have not returned to normal.</p> <p><b>Elderly:</b> There is no relevant use in the elderly population for the recommended indication.</p>
<b>Contra- indications</b>	<ul style="list-style-type: none"> <li>Hypersensitivity to the active substances or to any of the excipients.</li> <li>Venous thromboembolic disorder, past or present (e.g. deep venous thrombosis, pulmonary embolism).</li> <li>Arterial thromboembolic cardiovascular disease, past or present (e.g. myocardial infarction, cerebrovascular accident, ischemic heart disease).</li> <li>Known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency or activated protein C (APC)-resistance, including Factor V Leiden).</li> <li>Known osteoporosis.</li> <li>Headaches with focal neurological symptoms or migraine headaches with aura.</li> <li>Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).</li> <li>Presence or history of liver tumours (benign or malignant).</li> <li>Presence or history of severe hepatic disease as long as liver function values have not returned to normal.</li> <li>Pregnancy or suspected pregnancy and breastfeeding.</li> </ul>

	<ul style="list-style-type: none"> <li>• Genital bleeding of unknown aetiology.</li> <li>• Concomitant use of hormonal contraceptives.</li> <li>• Contains lactose: patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Ryeqo®.</li> </ul>
<p><b>Cautions</b> (see <a href="#">SPC</a> for full details)</p>	<ul style="list-style-type: none"> <li>• Prior to the initiation or reinstatement of treatment, a complete medical history (including family history) must be taken. Blood pressure must be measured, and a physical examination must be performed. During treatment, periodic check-ups must be carried out according to standard clinical practice.</li> <li>• Stop any hormonal contraception prior to initiation of treatment. Non-hormonal methods of contraception must be used for at least 1 month after initiation of treatment and for 7 days following 2 or more missed consecutive doses.</li> <li>• Pregnancy must be ruled out prior to administering or re-initiating treatment.</li> <li>• Risk of thromboembolic disorders (see SmPC for risk factors for venous thromboembolism (VTE) and arterial thromboembolism (ATE), including).</li> <li>• Smoking is not advised due to risks of ATE.</li> <li>• Risk factors for osteoporosis / bone loss.</li> <li>• Liver test abnormalities. Discontinue treatment if jaundice develops.</li> <li>• Change in menstrual bleeding pattern. Seek advice and guidance if there are concerns about the pattern or extent of bleeding.</li> <li>• Reduced ability to recognise pregnancy.</li> <li>• Uterine fibroid prolapse or expulsion.</li> <li>• Mood changes / depressive symptoms. Discontinue if severe depression recurs.</li> <li>• Hypertension.</li> </ul>
<p><b>Adverse effects</b> (see <a href="#">SPC</a> for full details)</p> <p>▼ drug – report suspected adverse effects to the <a href="#">MHRA</a></p>	<ul style="list-style-type: none"> <li>• The most common adverse effects are headache, hot flush and uterine bleeding.</li> <li>• Other commonly reported side effects include irritability, dizziness, nausea, alopecia, hyperhidrosis, night sweats, arthralgia, vulvovaginal dryness and reduced libido.</li> <li>• Uncommon cases of dyspepsia, angioedema, urticaria, breast cysts, and uterine myoma expulsion.</li> <li>• Frequency not known: bone loss, embolism and thrombosis, uterine leiomyoma prolapse.</li> </ul>
<p><b>Pregnancy, lactation and fertility</b> (see <a href="#">SPC</a> for full details)</p>	<ul style="list-style-type: none"> <li>• Ryeqo® inhibits ovulation, and often causes amenorrhea, in women taking the recommended dose and provides adequate contraception.</li> <li>• Ovulation and menstrual bleeding will return rapidly after discontinuing treatment. An alternative method of contraception should start immediately after discontinuing treatment.</li> <li>• A non-hormonal contraceptive method is recommended for use for 1 month after initiation of treatment and for 7 days following 2 or more missed consecutive doses.</li> <li>• Concomitant use of hormonal contraceptives is contraindicated.</li> <li>• Use during pregnancy is contraindicated. Discontinue treatment if pregnancy occurs.</li> <li>• Breastfeeding is contraindicated during the use of Ryeqo® and for 2 weeks following discontinuation treatment.</li> </ul>
<p><b>Interactions</b> (see <a href="#">SPC</a> for full details)</p>	<ul style="list-style-type: none"> <li>• Concomitant use with oral P-gp inhibitors is not recommended. If concomitant use with once or twice daily oral P-gp inhibitors is unavoidable (e.g. azithromycin), take Ryeqo® first, and separate dosing with the P-gp inhibitor by at least 6 hours and monitor patients more frequently for adverse reactions.</li> </ul>

	<ul style="list-style-type: none"> <li>Co-administration with strong CYP3A4 and/or P-gp inducers is not recommended.</li> <li>Oestrogen and progestogen medicinal products may affect the metabolism of certain other active substances. Accordingly, plasma concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine) with use of Ryeqo®. Dose adjustment of these medicines may be necessary.</li> </ul>
<b>Counselling points</b>	<ul style="list-style-type: none"> <li>One tablet of Ryeqo® to be taken once daily, at about the same time with or without food with a little liquid.</li> <li>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.</li> <li>Non-hormonal methods of contraception must be used for at least 1 month after initiation of treatment.</li> <li>Ryeqo® should not be used at the same time as a hormonal contraceptive.</li> <li>Ovulation and menstrual bleeding will return rapidly after discontinuing treatment. A discussion with the patient, regarding appropriate contraceptive methods, must therefore take place prior to discontinuing treatment and alternative contraception needs to be started immediately after discontinuation of treatment.</li> <li>Provide information about <a href="#">missed doses</a> and <a href="#">adverse effects</a>.</li> <li>Advise patients to contact their doctor if they experience mood changes and depressive symptoms during treatment.</li> </ul>
<b>Dual X-ray absorptiometry (DXA) scans</b>	<ul style="list-style-type: none"> <li>It is the responsibility of the specialist to organise the necessary DXA scan(s).</li> <li>In patients with history of a low trauma fracture or other risk factors for osteoporosis or bone loss, a DXA scan is recommended prior to starting treatment. For additional information on osteoporosis risk factors, click <a href="#">here</a>.</li> <li>A DXA scan is recommended after 1 year of treatment to verify that the patient does not have an unwanted degree of bone mineral density loss, that exceeds the benefit of treatment. The decision to stop or continue treatment should be clearly communicated to the patient's GP.</li> <li>If there is no unwanted degree of bone mineral density loss, the patient can be discharged to the care of their GP (the specialist will remain available for any future queries).</li> </ul>
<b>References</b>	<ol style="list-style-type: none"> <li>SmPC for relugolix–estradiol–norethisterone (Ryeqo®), last updated 09 September 2024 <a href="https://www.medicines.org.uk/emc/product/12934/smpc">https://www.medicines.org.uk/emc/product/12934/smpc</a> [last updated: 09 September 2024].</li> <li>NICE TA832: Relugolix–estradiol–norethisterone acetate for treating moderate to severe symptoms of uterine fibroids, published 19 October 2022 <a href="https://www.nice.org.uk/guidance/ta832">https://www.nice.org.uk/guidance/ta832</a>.</li> <li>NICE TA1057: Relugolix–estradiol–norethisterone for treating symptoms of endometriosis, published 16 April 2025, <a href="https://www.nice.org.uk/guidance/ta1057">https://www.nice.org.uk/guidance/ta1057</a>.</li> <li>Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <a href="https://bnf.nice.org.uk/drugs/relugolix-with-estradiol-and-norethisterone-acetate/">https://bnf.nice.org.uk/drugs/relugolix-with-estradiol-and-norethisterone-acetate/</a> [Accessed on 11 February 2026].</li> <li>NICE Clinical Knowledge Summaries <a href="http://cks.nice.org.uk">http://cks.nice.org.uk</a> [Accessed on 11 February 2026].</li> </ol>

Version	Author	Purpose/Change	Date
1.0	Medicines Optimisation Team	New document	March 2026