NCPE Assessment Summary

Relugolix with estradiol and norethisterone acetate (Ryeqo®)

HTA 24018

28 April 2026

Applicant: Gedeon Richter

Ryeqo® (Relugolix with estradiol and norethisterone acetate)
for the symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of Ryeqo® (relugolix with estradiol and norethisterone acetate), herein referred to as relugolix combination therapy (relugolix CT).

Following assessment of the Applicant's submission, the NCPE recommends that relugolix CT (Ryeqo®) not be considered for reimbursement, for this indication, unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Gedeon Richter) Health Technology Assessment of relugolix CT (Ryeqo®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In July 2025, Gedeon Richter submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of relugolix CT (Ryeqo®) for the symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis. Gedeon Richter is seeking reimbursement of relugolix CT on the High-Tech Drug Arrangement.

Endometriosis is a chronic inflammatory condition, characterised by the presence of endometrial-like tissue outside of the uterus, commonly linked to pelvic pain and infertility. Patients with endometriosis typically present with a wide range of symptoms, including pain during menstruation (dysmenorrhoea), pain during intercourse (dyspareunia), non-menstrual pelvic pain (NMPP), pain at ovulation, pain when defecating (dyschezia), pain during urinating (dysuria), heavy menstrual bleeding, and chronic fatigue.

Relugolix CT (40mg/1mg/0.5mg) is a fixed-dose combination, once daily, oral tablet containing gonadotrophin releasing hormone (GnRH) antagonist (relugolix), an oestrogen receptor agonist (estradiol), and a progestogen (norethisterone acetate). Relugolix decreases the release of luteinising hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland. The reduction in FSH prevents follicular growth, thereby reducing oestrogen production. Prevention of an LH surge inhibits ovulation and development of the corpus luteum, which precludes production of progesterone. Estradiol alleviates symptoms associated with a hypo-estrogenic state, such as vasomotor symptoms and bone mineral density (BMD) loss associated with the pharmacological action of GnRH inhibition. Norethisterone acetate reduces oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised patients. Therefore, relugolix CT reduces symptoms of endometriosis-associated pain. In addition, Relugolix CT provides contraception when taken for at least one month. The treatment duration for relugolix CT is indefinite. Discontinuation should be considered when the patient enters menopause, as the symptoms of endometriosis are expected to regress when menopause begins.

The Applicant considered GnRH agonists (i.e., triptorelin acetate, leuprorelin acetate) to

be relevant comparators to relugolix CT. Add-back therapy (ABT) (i.e., tibolone, combined hormonal replacement therapy) was assumed to be used in all patients treated with GnRH agonists to prevent associated side effects. The Review Group also considered surgery (i.e., conservative surgery such as laparoscopy or hysterectomy) to be a relevant comparator; however, surgery was not included by the Applicant, which is considered a limitation of the assessment.

1. Comparative effectiveness of relugolix CT

The efficacy and safety of relugolix CT was assessed in two similarly designed phase III, double-blind, randomised controlled trials (SPIRIT 1 and SPIRIT 2). Participants who completed the SPIRIT 1 or SPIRIT 2 trials were eligible to enrol in the 80-week open-label extension (SPIRIT OLE).

Participants were randomised to relugolix CT once daily for 24 weeks or relugolix 40mg monotherapy once daily for 12 weeks followed by relugolix CT for 12 weeks (delayed relugolix CT), or placebo for 24 weeks. The delayed relugolix CT treatment arm is not the focus of this report and is not discussed further. Co-primary endpoints included the proportion of participants who met the responder criteria for dysmenorrhea and NMPP at week 24 or end of treatment. Dysmenorrhea response was defined as achieving a mean reduction of at least 2.8 points on the dysmenorrhea Numerical Rating Scale (NRS) with no increase in analgesic use. NMPP response was defined as achieving a mean reduction of at least 2.1 points on the NMPP NRS with no increase in analgesic use. In both SPIRIT 1 and SPIRIT 2, a statistically significantly higher proportion of dysmenorrhea and NMPP responders was observed in the relugolix CT arm vs the placebo arm (SPIRIT 1: dysmenorrhea: 74.5% vs 26.9%; NMPP: 58.5% vs 39.6%; SPIRIT 2: dysmenorrhea: 75.2% vs 30.4%; NMPP: 66.0% vs 42.6%). SPIRIT 1 and SPIRIT 2 provided an overall power of at least 90% for each study to detect an absolute treatment difference of 20% for both co-primary endpoints simultaneously. A difference of at least 20% was considered to be clinically relevant by the Applicant. The results were considered clinically relevant by the CHMP who considered the benefit of treatment has been robustly demonstrated versus placebo. The effect of relugolix CT was sustained over the SPIRIT OLE treatment period (104 weeks). Limitations of SPIRIT 1, SPIRIT 2 and the SPIRIT OLE study include: the thresholds used in measuring the co-primary endpoints were not externally

validated and should be interpreted with caution; no direct comparative evidence with appropriate comparators is available as relugolix CT was compared to placebo (in SPIRIT 1 and SPIRIT 2); and the long-term efficacy of relugolix CT is unknown beyond 104 weeks (SPIRIT OLE).

2. Indirect Treatment Comparison (ITC)

Head-to-head trials were available to provide direct comparative evidence for relugolix CT versus placebo (considered a proxy for best supportive care [BSC]) from SPIRIT 1 and SPIRIT 2. Indirect comparative methods were required to inform the comparison between relugolix CT and the comparators of relevance. The Applicant provided an ITC evaluating the relative efficacy of relugolix CT versus GnRH agonists (with ABT); however, no ITC with surgery was provided. The Review Group considered this to be a limitation in interpreting the comparative efficacy of relugolix CT.

The ITC provided by the Applicant, included four placebo-controlled trials (SPIRIT 1, SPIRIT 2, D'Hooghe et al., and Osuga et al.). In SPIRIT 1 and SPIRIT 2 relugolix CT was the intervention, whereas the other trials included the GnRH agonist leuprorelin acetate in the intervention arm. The Review Group considered the co-primary endpoints of the SPIRIT 1 and SPIRIT 2 trials to be preferrable outcomes for use in the ITC; however, the Applicant declined to provide this functionality. Instead, different outcome measures including overall pelvic pain (OPP) and total pelvic pain (TPP) were used in the ITC. Due to the considerable heterogeneity in the scales used in the individual components of TPP across studies, the Applicant selected OPP only for use in the cost-effectiveness model (CEM). Based on the results of the ITC, relugolix CT is less effective than GnRH agonist treatment in treating pelvic pain (odds ratio 1.11 (95% credible interval 0.55, 1.94), although this result is not statistically significant. As there was considerable heterogeneity within the included trials, the Review Group considered the ITC results to be uncertain.

3. Safety of relugolix CT

The safety profile of relugolix CT is based on pooled data from SPIRIT 1 and SPIRIT 2 with treatment duration of 24 weeks and from the 80-week SPIRIT OLE study. The overall incidence of adverse events (AEs) at 24 weeks was higher in the relugolix CT arm (75.8%) versus the placebo arm (70.4%). AEs associated with a hypoestrogenic state (including hot

flush, hyperhidrosis, and vulvovaginal dryness) were reported at a greater frequency in the relugolix CT arm versus the placebo arm. The AE profile from the SPIRIT OLE study was consistent with SPIRIT 1 and SPIRIT 2. Most commonly reported drug-related AEs in patients treated with relugolix CT for up to 104 weeks were, headache (25.6%), hot flush (13.7%), and decreased BMD (9.0%). The SmPC recommends that clinicians perform a dual X ray absorptiometry scan after 12 months of relugolix CT treatment, and prior to starting treatment in patients with risk factors for osteoporosis or bone loss. Other potential risks observed with GnRH agonists and GnRH antagonists (such as relugolix CT) have been sufficiently characterised and warnings are included in the SmPC.

4. Cost effectiveness of relugolix CT

The Applicant compared the cost-effectiveness of relugolix CT to GnRH agonists (with ABT) in the base case. Surgery was not considered a comparator by the Applicant and was included in the CEM as a subsequent treatment option only.

Methods

The Applicant submitted a semi-Markov cohort model, which included 15 health states, and was complex in structure. The CEM had a lifetime horizon and a three-month cycle length. In each cycle, patients accrue QALYs and incur costs based on the utility (health-related quality of life) values and costs specified for the health state occupied, the relevant treatment arm, and the time to treatment discontinuation (TTD).

All patients start in the health state "Initial treatment". Treatment response is assessed in the CEM after three months and six months. Three different treatment responses are included: complete response, partial response, and non-response. The effectiveness of relugolix CT is captured in the ability to achieve and maintain a complete response, thereby delaying patient progression (i.e. delaying a worsening in dysmenorrhea or NMPP symptoms) and the need to switch treatment. Complete response is measured as NRS score reductions from baseline of 2.8 for dysmenorrhea and 2.1 for NMPP and no increase of analgesic use at six months ("change from baseline" response in both endpoints) from the SPIRIT 1 and SPIRIT 2 trials. Partial response relates to when patients have responded in either dysmenorrhea or NMPP after three months. Clinical opinion to the Review Group indicated that the response

definitions used in the SPIRIT 1 and SPIRIT 2 trials do not align with clinical practice, where the measurement of response may vary across centres.

Patients who do not fulfil the complete response criteria at six months move to "Non-response" and do not receive active treatment (i.e. assuming a stopping rule for relugolix CT based on treatment response). BSC includes initial hormonal therapies with or without analgesics. The Review Group consider the stopping rule highly uncertain as the SPIRIT 1 and SPIRIT 2 trials did not include a stopping rule; and the SmPC does not include a stopping rule. However, the Review Group noted that endometriosis is a recurring condition and if a response is not obtained, patients may require another treatment option (pharmacological or surgical). Therefore, the Review Group consider that although treatment might be stopped in clinical practice, the definition of response used may vary across centres. The Applicant declined the Review Group request to provide scenario analyses based on alternative stopping rule response thresholds.

A discontinuation rate over time was estimated from the time to treatment discontinuation reported in the SPIRIT OLE study. The estimated discontinuation rate was adjusted for cases who discontinued treatment due to protocol deviations or a desire to get pregnant. The Review Group considered that the unadjusted discontinuation rates as observed in the trials would have been more appropriate. Treatment duration is assumed to be six months for GnRH agonists although clinical opinion indicated that treatment with GnRH agonists may be longer in clinical practice.

Health-related quality of life (utility) values for participants entering the CEM at initial treatment, responders and non-responders were derived from the EQ-5D-5L data collected in SPIRIT 1 and SPIRIT 2, mapped to EQ-5D-3L data. The utility value for partial responders was assumed to be the mid-point of utility values for responders and non-responders. The increase in utility value assigned to non-responders compared to the baseline utility value lacks face validity. A scenario was explored by the Review Group whereby the utility for non-responders was changed to equal that of the utility at baseline. A long-term lower quality of life (disutility) of -0.18 was applied to all patients who underwent hysterectomy until menopause, beginning in the post-hysterectomy health states. This disutility was assumed to

be associated with infertility and other impacts of hysterectomy. The Review Group considered that women who have undergone a total hysterectomy may have a lower quality of life. At Preliminary Review the Applicant conducted a face validity check for disutility associated with infertility in a targeted literature search, which indicated that a plausible range for this disutility is between -0.03 and -0.07 (mean value: –0.05).

Results

An incremental analysis of the costs and benefits of relugolix CT versus GnRH agonists was presented by the Applicant. The probabilistic results, which were estimated for 1,000 simulations, are stable and similar to the deterministic results. **Table 1**

Table 1: Applicant base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
GnRH agonist	19,839	7.38	-	-	-
Relugolix CT	23,004	8.12	3,165	0.74	4,266

GnRH: gonadotropin-releasing hormone; **CT**: combination therapy; **QALY**: quality adjusted life year; **ICER**: incremental cost-effectiveness ratio

[a] Corresponding probabilistic ICER using 1,000 iterations =€3,890/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discounts of 4% on costs and QALYs apply.

[b] A commercial in confidence PAS has been proposed for relugolix CT, not included here.

The NCPE Review Group identified several limitations in the Applicant's base case and have made changes in the NCPE-adjusted base case. These include: changing the long-term disutility applied to patients who underwent hysterectomy from -0.18 to -0.05 (based on the face validity check), removing the stopping rule applied to non-responders at six months for relugolix CT (in the absence of any stopping rule in the clinical trials or SmPC), and changing the adjusted discontinuation rates to unadjusted discontinuation rates (to align with the intention-to-treat approach of the clinical trials). **Table 2**

Table 2: NCPE adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
GnRH agonist	20,624	8.48	-	-	-
Relugolix CT	25,083	8.32	4,459	-0.16	Dominated (more costly/less effective)

GnRH: gonadotropin-releasing hormone; **CT**: combination therapy; **QALY**: quality adjusted life year; **ICER**: incremental cost-effectiveness ratio; **NCPE:** National Centre for Pharmacoeconomics

[a] Corresponding probabilistic ICER using 1,000 iterations =Dominated. Figures in the table are rounded, and so calculations may not be directly replicable. Discounts of 4% on costs and QALYs apply.

[b] A commercial in confidence PAS has been proposed for relugolix CT, not included here.

Sensitivity analysis

The probabilities of cost-effectiveness for relugolix CT, versus GnRH agonists, in the Applicant base case was 100% at the €20,000/QALY threshold and the €45,000/QALY threshold. The probabilities of cost-effectiveness, in the NCPE adjusted base case, were 6.90% at the €20,000/QALY threshold and 9.00% at the €45,000/QALY threshold. A price-ICER analysis was not applicable for the NCPE adjusted base case as relugolix CT is dominated by GnRH agonists (i.e. relugolix CT is more costly and less effective than GnRH agonists).

5. Budget impact of relugolix CT

The price to wholesaler for one pack (28 oral tablets) of relugolix CT 40mg/1mg/0.5mg is €81.29 (VAT not applicable). The estimated total cost, per patient, per year of relugolix CT is €1,794.16 (VAT not applicable). The Applicant derived the eligible patient population for the number of women in Ireland with endometriosis using the Central Statistics Office population projections for women aged 18 to 51 years and applying UK incidence and prevalence data from the Health Improvement Network. The Applicant assumed that 55% of women will have a history of prior medical treatment, and were therefore eligible for treatment with relugolix CT. The Applicant assumed a market share of 6.8% in year one for relugolix CT, increasing to 71.0% in year five. The Applicant estimated 241 patients would be eligible to receive relugolix CT in year one, increasing to 2,618 patients in year five.

The Review Group note that relugolix CT is a combination-therapy oral tablet, while GnRH agonists are given by injection and must be co-administered with ABT, and surgery is an invasive treatment option. Uptake might be expected to be high. The cumulative five-year gross drug budget impact is €11.0 million (VAT not applicable). The cumulative five-year net drug budget impact is €8.8 million (including VAT).

Relugolix CT is licensed but not reimbursed for treatment of uterine fibroids. Thus, should relugolix CT be reimbursed, the HSE may consider the need to implement processes to facilitate prescribing for the indication under consideration here.

6. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

7. Conclusion

The NCPE recommends that relugolix CT (Ryeqo®) not be considered for reimbursement, for this indication, unless cost-effectiveness can be improved relative to existing treatment*.

The Applicant's stopping rule is the key driver within the cost-effectiveness analysis, and when implemented in the Applicant base case, relugolix CT is a cost-effective treatment option compared to standard of care. Relugolix CT is a less effective and more costly treatment option when the stopping rule is removed.

*Next steps: The NCPE Assessment Report and recommendation, will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.
Further information on this process may be found here.