NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Relugolix–estradiol–norethisterone for treating symptoms of endometriosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using relugolix combination therapy (CT) in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using relugolix CT in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 22 April 2024
- Second evaluation committee meeting: 08 May 2024
- Details of membership of the evaluation committee are given in section 4.

1 Recommendations

1.1 Relugolix–estradiol–norethisterone (relugolix combination therapy [CT]) is not recommended, within its anticipated marketing authorisation, for treating symptoms of endometriosis in adults who have had medical or surgical treatment for their endometriosis.

1.2 This recommendation is not intended to affect treatment with relugolix CT that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

After pain relief and hormonal treatment, usual treatment options for endometriosis are gonadotropin-releasing hormone (GnRH) agonists and surgery. There is no cure for endometriosis, and there is an unmet need for long-term and non-invasive (non-surgical and not injected) treatments for its symptoms.

Clinical trial evidence shows that relugolix CT reduces pain compared with placebo. Relugolix CT has not been directly compared in a clinical trial with usual treatment. Indirect comparisons suggest that it is likely to reduce pelvic pain almost as well as GnRH agonists, but this is uncertain. It is also uncertain how well relugolix CT works compared with surgery.

There are also concerns about the economic model. This is because of uncertainty about the completeness of the clinical evidence, and the absence of evidence on other usual treatments.

Because of the uncertainties in the clinical evidence and economic model, it is not possible to determine the most likely cost-effectiveness estimates for relugolix CT. So, it is not recommended.

2 Information about relugolix CT

Anticipated marketing authorisation indication

2.1 Relugolix–estradiol–norethisterone (relugolix CT) (Ryeqo, Gideon Richter) does not yet have a marketing authorisation in Great Britain. It received a marketing authorisation from the European Commission for the 'symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis'.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for relugolix CT.

Price

2.3 The list price for relugolix CT is £72 per pack of 28 tablets (excluding VAT; BNF online, accessed March 2024).

3 Committee discussion

The evaluation committee considered evidence submitted by Gideon Richter, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Endometriosis is a chronic, long-term condition in which the tissue that normally lines the womb (endometrium) grows elsewhere in the body. When this tissue breaks down in a normal menstrual cycle, it can become trapped in the pelvis. The exact cause of endometriosis is not known, but it is mediated by hormones and so is associated with menstruation. Endometriosis occurs during the reproductive phase of life but also sometimes beyond the menopause. Clinical experts noted that, despite its high prevalence, there is a lack of disease awareness among patients,

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healthcare providers, and the public. They noted limited understanding of endometriosis with a lack of funding and research in the area. Both patient and clinical experts highlighted issues with delayed diagnosis and in accessing services in clinical practice. The average time from onset of symptoms to diagnosis is around 9 years. Diagnosis can involve a laparoscopy (thin tube with a camera on the end) or may be less invasive such as ultrasound or MRI.

Effects on quality of life

3.2 Symptoms can vary depending on the extent and location of the endometrial tissue but the most common is chronic pain. Other symptoms can include painful periods, subfertility and fatigue. The patient experts noted how debilitating endometriosis is and that it impacts day-to-day life. Endometriosis can have a significant physical, sexual, psychological and social impact, and affect productivity and ability to work. The committee concluded that endometriosis has a significant impact on quality of life for people with the condition.

Clinical management

Treatment options

3.3 There is no cure for endometriosis so current treatments aim to improve quality of life and maximise fertility for people for whom this is important. As the severity of symptoms can fluctuate over time, the treatment pathway is fluid. Treatment selection is strongly led by patient choice. For example, treatment choice may differ if fertility is a priority (see NICE's guideline on endometriosis, NG73). Current first-line treatment is a short-term trial of analgesics (including paracetamol or non-steroidal anti-inflammatory drugs [NSAIDs] together or alone), neuromodulators (in line with NICE's guideline on neuropathic pain, CG173), or hormonal treatments. But all current hormonal treatments are contraceptive, so are not suitable for those wishing to conceive.

3.4 If first-line treatments do not address symptoms, the clinical experts noted that people could be offered gonadotropin-releasing hormone (GnRH) agonists, with add-back therapy unless contraindicated or unnecessary, or conservative surgery (excision or ablation). GnRH agonists can also sometimes be used to delay the need for surgery. The company noted that GnRH agonists are only licensed for 6 months with add-back therapy but are used for longer in clinical practice. The clinical and patient experts noted that GnRH agonists are usually administered by injection every 1 to 3 months, so people have to travel for regular injections. A patient expert added that some GPs do not feel comfortable administering GnRH agonists, so people have to travel to a hospital, adding more burden. And some GPs will not prescribe GnRH agonists for longer than the licence.

3.5 A clinical expert noted that endometrial tissue often grows back, with 20% of people having disease recurrence after 2 years, and 40% to 50% of people after 5 years. So sometimes surgery needs to be repeated. They noted that there can be long waiting times for surgery and it can be associated with side effects like neuropathic pain after multiple operations. Once people have tried other treatments, hysterectomy can be considered, but only some people would consider this as an option.

3.6 The clinical experts noted that best supportive care is typically used alongside other treatments to improve quality of life. It is usually multi-modal and can include physiotherapy, psychological support, acupuncture and osteopathy, nutrition and dietary changes, analgesics such as paracetamol, codeine, NSAIDs, transcutaneous electrical nerve stimulation (TENS), lidocaine patches, and opiates. A clinical expert added that some of these treatments may be self-funded. The committee concluded that there is an unmet need for licensed, long-term, non-invasive and effective treatment options to manage symptoms of endometriosis. It added that people with the condition and clinicians would welcome a new treatment option.

Comparators

3.7 The company positioned relugolix–estradiol–norethisterone (relugolix combination therapy [CT]) as a second-line treatment after NSAIDs, neuromodulators and surgery, and considered GnRH agonists the most relevant comparator. The EAG agreed that GnRH agonists are relevant comparators. The EAG's clinical expert had noted that nasal or parenteral GnRH agonists are available, but the clinical expert at the meeting was unaware of them being used. The clinical experts noted that given the fluctuating treatment pathway, like GnRH agonists, relugolix CT may be used at different points in the pathway. The EAG's clinical experts had also considered that relugolix CT could be used at the second or third line. The clinical expert at the meeting agreed, noting it would likely be used if hormonal contraceptives, progestogens, or surgery were ineffective. They added that surgery is generally used at second and third line. The clinical experts summarised that relugolix CT could be used as an alternative to either GnRH agonists or surgery, as a bridge to surgery in the short term as part of combination treatment for symptom relief (in line with NG73), for a longer period if there is a wait for surgery, or after surgery to help with ongoing pain management. The clinical expert noted that interpreting the existing literature about surgical treatment is challenging because of the variable quality of the evidence, different definitions of surgery, and not capturing evolving expertise in surgical skills. The EAG highlighted a lack of clarity about the line of treatment, previous treatments and the population eligible for relugolix CT, all of which have implications for the relevant comparator. It noted that other comparators may be relevant. The committee therefore considered surgery a relevant comparator. The committee concluded that GnRH agonists and surgery were both relevant comparators in NHS clinical practice.

Clinical effectiveness

Systematic literature review

3.8 The EAG indicated that the company's systematic literature review was not methodologically robust. The EAG noted general poor reporting and lack of transparency relating to the date span on the Embase search, data extraction process and plan, quality assessment process and risk of bias assessment. It also questioned the appropriateness of the search methods and noted that the number of Embase search results (around 500) was unexpectedly small for a common condition. At clarification, the company updated a Cochrane systematic review (Veth et al., 2023) of GnRH analogues for endometriosis instead of conducting a new review because of time constraints. The company did not include any additional studies because none met the inclusion criteria. The EAG commented that the update to the Cochrane review was unsuitable, noting that the review covered different comparators and outcomes from the appraisal scope. It also noted a general lack of reporting for the update to the Cochrane review and also that there were fewer search results than expected. The EAG stated that a de novo systematic literature review addressing the decision problem of the evaluation was needed, and that this was likely to identify a different evidence base that could affect the committee's deliberations. The committee was concerned about the robustness of the literature review and the potential implications for the economic evaluation, which relied on the clinical effectiveness data identified. It noted also that only some search terms for surgery were included in the company's original review, and the Cochrane review excluded trials with surgery as a comparator (see section 3.7). The committee concluded that the lack of a robust systematic literature review created uncertainty about the effectiveness of relugolix CT compared with the relevant comparators, and other data included in the model. It considered an updated systematic literature review addressing these methodological issues and including evidence for all relevant comparators was needed to ensure the relevant evidence base has been identified.

Clinical trial evidence

3.9 The clinical evidence for relugolix CT was from 2 similar phase 3 double-blind randomised controlled trials, SPIRIT 1 and 2. The trials compared relugolix CT (n=212 and 208, respectively) with placebo (n=213 and 208, respectively) in pre-menopausal people aged 18 to 50 years with moderate to severe pain associated with endometriosis. The 2 co-primary outcomes were the proportion of people with dysmenorrhoea or non-menstrual pelvic pain whose condition responded to treatment. Response in dysmenorrhoea was defined as the mean reduction in numerical rating scale score of 2.8 points or more and no increase in use of analgesia. In the trials, a response was seen in 75% of people who had relugolix CT compared with 27% and 30% of people who had placebo at 24 weeks ($p<0.0001$) in SPIRIT 1 and SPIRIT 2, respectively. Response in non-menstrual pelvic pain was defined as a mean reduction in numerical rating scale score of 2.1 points or more and no increase in use of analgesia. In the trials, a response was seen in 59% and 66% of people who had relugolix CT compared with 40% and 43% of people who had placebo at 24 weeks ($p <0.0001$) in SPIRIT 1 and SPIRIT 2, respectively. Results from the clinical evidence were not presented in the EAG report because of the EAG's concerns with the completeness of the systematic literature review (see section 3.8). The committee concluded that, based on the direct comparative evidence, relugolix CT appeared to be more effective than placebo at reducing dysmenorrhoea and non-menstrual pelvic pain associated with endometriosis.

Indirect comparison

3.10 There were no trials directly comparing relugolix CT with any of the relevant comparators. The company did an indirect treatment comparison with the GnRH agonist leuprorelin acetate because it was the only GnRH agonist that could be connected with relugolix CT in a network. The company conducted a comparison for 2 outcomes: overall pelvic pain, and total pelvic pain (a composite measure of dysmenorrhoea, non-menstrual

pelvic pain and dyspareunia). For both outcomes, SPIRIT 1 and 2 outcomes were pooled for relugolix CT. The comparison of overall pelvic pain included data from D'Hooghe et al. (2019) (n=540) which compared leuprorelin acetate with placebo. The indirect comparison, which was linked using the placebo arm of both trials, showed no differences between relugolix CT and leuprorelin acetate in overall pelvic pain (odds ratio [OR] 1.1, 95% credible interval [CrI] 0.032 to 41). The comparison of total pelvic pain included 2 trials to connect leuprorelin acetate with relugolix CT. Strowitzki et al. (2010) (n=252) compared leuprorelin acetate with dienogest and Lang (2018) (n=255) compared dienogest with placebo. The placebo arm from Lang (2018) was connected with the placebo arm of the SPIRIT trials to make the comparison between leuprorelin acetate and relugolix CT. The indirect comparison showed no differences between relugolix CT and leuprorelin acetate in total pelvic pain (OR 2.5, 95% CrI 0.032 to 190). The relative effect from the analysis on overall pelvic pain was used in the model to derive response rates for GnRH agonists. The committee concluded that an indirect comparison was appropriate in the absence of direct head-to-head trials. It concluded that although there appeared to be minimal difference between GnRH agonists and relugolix CT, there was uncertainty because it was not clear if all the relevant evidence on GnRH agonists was identified from the systematic literature review (see section 3.8). The committee also noted uncertainty about the relative efficacy of surgery, which was also considered a relevant comparator, but was not included in the analyses (see section 3.7).

Economic model

Company's modelling approach

3.11 The company presented a semi-Markov cohort model with 12 unique health states based on response to medical or surgical treatments. The model cycle was 3 months. Response to initial treatment was evaluated after 6 months. People who did not respond to treatment switched to best

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supportive care or surgery. Before surgery, there was also a distinct period of time during which people had best supportive care while waiting for surgery. The committee noted that the treatment pathway is likely more complex than was captured in the model structure. It concluded that the model should reflect the treatment pathway, including the use of best supportive care and all the relevant comparators, including surgery.

Best supportive care

3.12 The committee recalled that clinical experts had stated that best supportive care is used alongside all treatments (see section 3.6). The EAG also noted some confusion about the role of best supportive care in the model and whether it included analgesics, which the clinical experts confirmed it likely would. The EAG noted that response to best supportive care was taken from the placebo arm of the SPIRIT trials but it was not clear if this treatment arm included analgesics, since one of the trial aims was to reduce analgesic usage. Also, the company stated analgesics were used alongside all treatments. The committee concluded that more clarity was needed on how best supportive care is defined and modelled.

Duration of GnRH agonist treatment

3.13 In the company's model, relugolix CT was given for up to 16 years and GnRH agonists were given for up to 1 year, with add-back therapy added after the first 3 months. The committee recalled that GnRH agonists are licensed for 6 months but are used longer in clinical practice (see section 3.4). The EAG noted that the relative clinical effectiveness had minimal impact in the model because GnRH agonists were taken for a short time compared with relugolix CT. The committee was concerned that the duration of GnRH agonists used in the model may not reflect clinical practice. The clinical experts agreed that GnRH agonists were used beyond their licensed treatment duration in clinical practice, with add-back therapy to prevent long-term complications, for example those related to bone health. The clinical and patient experts agreed that the length of time that GnRH agonists were used varied throughout the country (see section

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3.4). The clinical expert at the meeting was aware of many professionals prescribing GnRH agonists for longer than 5 years and some even up to 10 years, particularly for younger people. The committee acknowledged that the duration of GnRH agonist treatment varied and was concerned that the model may not reflect clinical practice. It noted that the company had done scenario analyses increasing the length of GnRH agonist treatment to 2 years, and that this had had a minimal impact on the results. The committee concluded that it would prefer to see sensitivity analysis using longer treatment durations for GnRH agonists to reflect variations in clinical practice.

Clinical outcomes used in the model

3.14 The model used the co-primary endpoints from the SPIRIT trial (the proportion of people whose non-menstrual pelvic pain or dysmenorrhoea responded to treatment; see section 3.9) to derive response rates for relugolix CT. To derive response rates for GnRH agonists, the OR from the indirect comparison for overall pelvic pain was applied to the response rates for relugolix CT. While acknowledging that the clinical evidence in the model had a minimal impact on the model results because of the difference in treatment duration between treatments, the EAG was concerned by the weak link between the clinical effectiveness and economic evidence. It considered that more clinical parameters capturing important outcomes were needed in the model. It noted that several outcomes from the scope were not reported in the SPIRIT trials and were not included in the model. These included endometriosis recurrence, hospital admission, fertility and complications. The company noted that endometriosis recurrence is not relevant since the disease is not 'cured' with treatment. It noted that complications were included in the model as adverse events. It added that hospital admission was most likely related to procedures that were already captured in the model. The clinical and patient experts agreed that pelvic pain, including chronic pain and dysmenorrhoea, and dyspareunia were all outcomes that affect quality of life and are important to people with endometriosis. The patient expert

also highlighted the importance of the psychological impact of this chronic condition. The committee concluded that more dimensions that are important to patients' quality of life and costs should be included in the model.

Treatment effect waning

3.15 In the company base case, people took relugolix CT until they had a response to treatment, stopped treatment, or reached menopause (if their condition responded to treatment). The response was assumed to remain constant over time. The company cited evidence from the open-label extension of the SPIRIT trials which reported high response rates (84.8% for dysmenorrhoea and 75.8% for non-menstrual pelvic pain) after 104 weeks or the end of treatment. The company explained that treatment waning was captured through the discontinuation rate applied to the model when people moved from complete response to non-response. The EAG judged a 15-year sustained treatment effect to be a strong assumption. It noted that it was unclear if this was captured through the discontinuation rate, because the company assumed a constant discontinuation rate after 15 months and that best supportive care and surgery were both effectively the comparator after GnRH treatment stopped at a year. It stated that sensitivity analyses to explore this assumption would be important. The clinical expert at the meeting noted that the treatment effect of GnRH agonists does not appear to wane. In the absence of longer-term evidence for the constant treatment effect with relugolix CT, the committee considered that it may be appropriate to assume that the reported constant treatment effect from GnRH agonists applies to relugolix CT on the basis of a similarity in the mechanisms of action of GnRH agonists and antagonists. It also concluded that scenarios examining the impact of treatment waning would be helpful.

Model validation

3.16 In addition to the EAG's overall concerns about the model missing potentially important comparators, the EAG also commented that the

validation of the model was not sufficient and that it produced counterintuitive results. The EAG explained that the model structure was unclear, overly complex and that it was unable to fully validate and critique the model because it was not a de novo model, but instead was an adapted model containing parameters that were not used in this submission. It also highlighted that the company had explained that the similarities in the probabilistic and deterministic results indicated that it was a robust analysis. But the EAG stated that there was a lack of transparency about the probabilistic sensitivity analysis and noted that there may have been some missing parameters and parameter-specific variation. The committee was concerned about similar probabilistic and deterministic results being interpreted to indicate robust results, noting that this is not a correct interpretation of the results. The EAG also noted several instances of results that appeared counterintuitive. For example, when the proportion of people having relugolix CT with complete response decreased, relugolix CT was cost saving compared with GnRH agonists. The company explained in the meeting that the cost per patient was cheaper with relugolix CT when the cost of administering the injection for GnRH agonists was included before the first assessment at 6 months (see section 3.11). It noted that in the base case, all increased costs for relugolix CT were driven by responses to relugolix CT and so these people would have treatment for longer than with GnRH agonists. So if the response rates for relugolix CT were decreased, the costs for relugolix CT would also decrease. The quality-adjusted life years (QALYs) were still higher with relugolix CT than with GnRH agonists because the 'responders' remained on treatment for much longer than people who had GnRH agonists. The EAG also noted that if 100% of people stopped relugolix CT at 9 or 12 months, having relugolix CT resulted in more QALYs and fewer costs. The EAG considered this counterintuitive because the OR of 1.1 suggested GnRH agonists were more effective in the first year of model. The company responded that it was unable to replicate the same output with the same change. The committee

concluded that full model validation was needed, including greater transparency about how the probabilistic sensitivity analyses were done, and a clear justification of counterintuitive results.

Utility values

Utilities used in model

3.17 In its model, the company used a baseline utility value of 0.58 across both treatment arms based on the SPIRIT trials, which included pre-menopausal people with moderate to severe pain associated with endometriosis. The EAG considered this to be low and noted that it came from a very wide range reported in the literature (0.15 and 0.78). Overall, the EAG was concerned about the face validity of the utility values used, noting that this contributed to overall uncertainty in the model. It wished to see scenarios considering different utility values. During the committee meeting, the company noted that the 0.58 value was chosen as the base case because the 0.78 utility value was reported in a prospective study of people having progestin, for whom treatment had already failed, which was not the relevant population for this topic. The committee noted that although the 0.58 value did reflect the trial population, the anticipated marketing authorisation covered any symptoms of endometriosis with previous medical or surgical treatment. The committee also noted that a utility value for non-response to treatment was around 0.72, which seemed large compared with the initial treatment utility value. The company explained that because of the definition of response there would be some people who did not meet the threshold for response in the clinical trial but who would have experienced some response, which is why some ‘responders’ had a higher utility value. The clinical expert noted that there are aspects to pain other than its severity (for example, pain in the bladder, bowel, migraine, chronic fatigue). The committee concluded that there was overall uncertainty in the utility values used in the model because of the range of values, small differences in utility values for response and non-response, and inconsistency in the value chosen and

the population in the decision problem. The committee considered that more clarity and validation was needed about each of the values provided.

Long-term utility and disutility

3.18 The EAG noted that the model was relatively insensitive to changes to utility values for response and non-response health states and that most QALY gains in the model were from disutilities from surgery (0.606 of 0.71 QALYs). It noted some uncertainty around some of the longer-term utilities and disutilities in the model. For example, the studies used to inform disutility for adverse events from surgical complications were very old. While the company considered this would have a minimal impact on the results, the EAG disagreed. The EAG also noted that it was unclear if disutility values used for hysterectomy were applicable to the UK, noting they were from the Global Burden of Disease study published in 1990. Also, the EAG noted that the company used an additive approach to applying disutilities from adverse events and surgery-related complications, whereas a multiplicative approach is usually preferred (see section 4.3.7 of the NICE health technology evaluations manual). It stated that the company should justify its approach and explore the impact with scenario analyses. The committee understood that the QALY gain was driven by disutilities. Because the cost effectiveness was largely determined by the longer-term utility values used in the model, and because there was a possibility that the age of the source of some utility values in the model may mean it was not generalisable to current practice, it concluded that there was a high level of uncertainty with the utility values used in the model. And basing a decision on a model with a high level of uncertainty increases the potential for decision error. It also concluded that a multiplicative approach to applying disutilities from adverse events should be used.

Disutility from infertility

3.19 The company did not explicitly model the disutility from infertility related to having a contraceptive treatment. It considered that any differences in

utility because of infertility between treatments would have been captured in the EQ-5D measurements in the trial. However, the EAG believed the impact on infertility could be greater for people taking relugolix CT because the treatment was given for longer. It also considered that the impact on fertility of stopping treatment after 1 year may differ from stopping treatment after 16 years of treatment. The company explained that the utility benefit after stopping relugolix CT was too uncertain to parameterise because the time to regain fertility between treatments was likely only months. The company excluded people who stopped treatment because of pregnancy or who wished to conceive from discontinuation rates because it considered best supportive care and surgery were not feasible options for these people. The EAG was unclear why best supportive care and surgery, which can be conservative, were not considered feasible options for these people. It noted it was unclear if people who wished to become pregnant were included in the model, and the impact of including these people was unknown. The EAG also noted that the model applied utility decrements to all people after hysterectomy, but it preferred that the decrement only be applied to people who were actively seeking to have become pregnant and that it should be age-dependent and based on a more recent estimate (see section 3.18). Overall, the EAG considered the company's approach to capturing disutility from infertility too simplistic, particularly since fertility drives treatment choice (NG73). The EAG noted that based on the model structure, disutility from fertility had a big impact on the results. It explained, for example, that decreasing the disutility value associated with infertility by half doubled the cost-effectiveness estimates. The clinical expert at the meeting noted that GnRH agonists also affect infertility and noted that neither treatment would be taken by people who wished to conceive. The committee acknowledged the uncertainty around how infertility was incorporated into the model. It concluded it would have preferred to see scenarios in which the disutility from infertility was explored separately to better capture in the population that will have

treatment in the NHS (for example, by capturing that not all people want to have children).

Cost-effectiveness estimates

Company cost-effectiveness estimate

3.20 Because of confidential commercial arrangements for the comparator, the exact cost-effectiveness estimates are confidential and cannot be reported here. The company's incremental cost-effectiveness ratios (ICERs) for relugolix CT compared with GnRH agonists were within what is normally considered a cost-effective use of NHS resources. The EAG did not provide a base case because it had serious concerns with the systematic literature review (see section 3.8) and the model validation (see section 3.16), and it considered that relevant comparators were missing from the analyses (see section 3.7), all of which would require major changes to the model, which was not possible with the existing evidence base.

Acceptable ICER

3.21 NICE's manual on health technology evaluations notes that, below a most plausible ICER of £20,000 per QALY gained, the decision to recommend a technology is normally based on the cost-effectiveness estimates and the acceptability of a technology as an effective use of NHS resources. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented, for example because of its view on the plausibility of the inputs to the economic modelling or the certainty around the estimated ICER, or both. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty about the inputs to the economic model, specifically the:

- efficacy of relugolix CT compared with GnRH agonists and the comprehensiveness of the evidence base supporting the indirect comparison (see sections 3.8 and 3.10)

- efficacy of relugolix CT compared with surgery (see sections 3.7, 3.8 and 3.10)
- clinical outcomes used in the modelling (see section 3.14)
- utility and disutility values (see sections 3.17 to 3.19).

The committee also considered the uncertainty in the cost-effectiveness estimates, including the:

- potential impact of better capturing the treatment pathway in the model, including the role of best supportive care as used in clinical practice (see sections 3.6, 3.11 and 3.12)
- potential impact of longer treatment durations for GnRH agonists in the model (see section 3.13)
- validity of the model outputs (see section 3.16).

The committee stated that if the company was able to provide evidence to overcome the uncertainties in the inputs and cost-effectiveness estimates, an acceptable ICER would be around £20,000 per QALY gained.

The committee's additional requests

3.22 The committee could not provide a preferred ICER because of its concerns about the completeness of the evidence and the relevant comparators (see sections 3.7 and 3.8). The committee would like to see the following:

- a systematic literature review addressing the methodological issues and including evidence for all relevant comparators (see sections 3.7 and 3.8)
- evidence on the efficacy of relugolix CT compared with surgery (see sections 3.7, 3.8 and 3.10)
- clarity about what constitutes best supportive care and how it is used in the model (see section 3.12)

- a model that more accurately reflects the treatment pathway including relevant comparators (see section 3.7) and use of best supportive care (see section 3.12)
- scenarios using longer treatment durations for GnRH agonists (see section 3.13)
- further validation and justification of the utilities used in the model and scenarios considering the impact of changing these values, for example, of baseline utility (see section 3.17)
- a multiplicative approach to incorporating disutilities from adverse events (see section 3.18)
- scenarios considering the EAG's preferred approach to capturing the disutility from infertility (see section 3.19)
- scenarios considering the impact of treatment waning (see section 3.15)
- full model validation and justification of any counterintuitive results (see 3.16).

Other factors

Equality

3.23 Several equalities issues were identified by stakeholders:

- The technology should be available to all eligible people, which may include trans men and non-binary people.
- People from ethnic minority backgrounds may be underdiagnosed or present later, with more severe symptoms. They may also receive a lower quality of care.
- General issues of underdiagnosis of endometriosis (see section 3.1).
- Contraceptive treatments may not be acceptable for people from some religious or ethnic backgrounds.
- Delaying childbearing either by choice or because of subfertility may be a risk factor for endometriosis.

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- Current treatment is sometimes dependent on the knowledge of individual healthcare professionals and regional variability.
- Clear and culturally competent information is needed to improve access.
- The SPIRIT trials included few people from ethnic minority backgrounds.
- Convenience of relugolix CT compared with GnRH agonist injections may particularly benefit some people, for example those with transportation barriers or mobility issues.

Race, religion, gender reassignment and disability are protected characteristics under the Equality Act 2010. The committee considered the potential equality issues, noting that its recommendation applies to all people within the marketing authorisation indication for relugolix CT for endometriosis. It concluded that its recommendations do not have a different impact on people protected by the equality legislation than on the wider population.

Uncaptured benefits

3.24 A clinical expert considered that relugolix CT is a step-change in the management of endometriosis. This was because the oral administration allows the medication to be taken at home. The committee recalled that GnRH agonists are usually taken by injection in a clinical setting, and considered that relugolix CT would give people more autonomy. The patient experts also highlighted the benefit of an all-in-one daily tablet that includes hormone replacement therapy, which means that a person does not have to remember to take add-back therapy separately. Because relugolix CT is given daily and has a shorter half-life than GnRH agonists, it may be quicker to return to normal hormonal levels after stopping treatment; this could be helpful for people wishing to recover fertility or people experiencing intolerable side effects. The clinical experts noted that there can be an initial flare of symptoms in the first few weeks with

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GnRH agonists that is not seen with relugolix CT. Clinical flares can lead to patients needing to be seen by healthcare providers or being admitted to hospital, and can lead to non-adherence to treatment. The committee concluded that there are additional benefits of relugolix CT for endometriosis that may not have been captured in the modelling but that some of them could be incorporated into an updated decision model.

Severity

3.25 NICE's advice about conditions with a high degree of severity did not apply.

Conclusion

Recommendation

3.26 The committee agreed that further information was needed to provide robust estimates of cost effectiveness for relugolix CT in current clinical practice. It considered that the clinical and economic evidence presented by the company was uncertain and likely not complete. It noted the reasons the EAG had not presented alternative cost-effectiveness estimates. Given the uncertainty, it would like to see additional analyses. The committee considered that there were no plausible cost-effectiveness estimates, and so was unable to recommend relugolix CT for treating symptoms of endometriosis.

4 Evaluation committee members and NICE project team

Evaluation committee members

This topic was evaluated as a single technology appraisal by the highly specialised technologies evaluation committee. The highly specialised technologies evaluation committee and the 4 technology appraisal committees are standing advisory committees of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel

Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Heather Stegenga

Technical lead

Elizabeth Bell

Technical adviser

Kate Moore

Project manager

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