NICE National Institute for Health and Care Excellence

NICE guidance

Relugolix–estradiol–norethisterone for treating symptoms of endometriosis

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendation

1.1 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.

What this means in practice

Relugolix CT must be funded in the NHS in England for the condition and population in the recommendation, if it is considered the most suitable treatment option. Relugolix CT must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that relugolix CT provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Why the committee made this recommendation

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 it is unclear how well relugolix CT works compared with surgery.

The cost-effectiveness estimates for relugolix CT compared with GnRH agonists and surgery are within the range that NICE considers an acceptable use of NHS resources. So, relugolix CT is recommended.

2 Information about relugolix CT

Marketing authorisation indication

2.1 Relugolix–estradiol–norethisterone (relugolix combination therapy [CT]; Ryeqo, Gedeon Richter) is indicated 'in adult women of reproductive age for 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 is 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 February 2025).

2.4 Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The evaluation committee considered evidence submitted by Gedeon 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, healthcare providers, and the public. They noted a 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. Patient experts emphasised that endometriosis affects individuals differently and no two people with endometriosis have the same experience. But 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) 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 (using a low dose of hormones at the same time as GnRH agonists to protect bones and minimise possible side effects) 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, 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 analgesics, neuromodulators, hormonal treatments and surgery. It stated GnRH agonists are the most relevant comparator and these are currently only available as injectable options. The EAG agreed that GnRH agonists are relevant comparators. The EAG's clinical expert had noted that unlicensed nasal or parenteral GnRH agonists are available, but the clinical expert at the first committee 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 explained 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. At consultation, the company stated that choice of treatments is guided by patient preference and medical history. The company did not include surgery as a comparator for relugolix CT. It explained that in NICE's technology appraisal guidance on relugolix CT for treating moderate to severe symptoms of uterine fibroids, surgery was not included as a comparator. The EAG stated that the current evaluation should reflect UK clinical practice, in which surgery could be a comparator for treating endometriosis after previous medical or surgical treatment. The clinical expert stated that patient choice and symptom management defines the choice of treatment. The patient expert also explained treatment choice is individualised and people may choose to have surgery or not at different stages in the treatment pathway, based on individual priorities. The committee noted that some surgical interventions would be comparators for relugolix CT. It concluded that for people who have had medical or surgical treatment for endometriosis, GnRH agonists and surgery are both relevant comparators in NHS clinical practice.

Clinical effectiveness

Systematic literature review

3.8 At the first meeting, the committee was concerned about the robustness of the systematic literature review and the potential implications for the economic evaluation, which relied on the clinical-effectiveness data identified. It also noted 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 decided 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. At consultation, the company did a new systematic

literature review that identified 139 reports (111 unique studies) including additional data on buserelin, goserelin, leuprorelin and triptorelin. It also identified long-term efficacy data from the SPIRIT open label extension study. The EAG noted the updated systematic literature review identified substantially more studies than the original, which identified 48 studies from 58 publications. It noted that the key limitations it had at the first committee meeting had been addressed. It advised the revised searches were appropriate. The committee concluded it was satisfied that the company's updated literature review and searches had identified the relevant evidence for decision making.

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 SPIRIT 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. At consultation, the company provided data from the SPIRIT open label extension study. At week 52, there was an 83.9% reduction from baseline in mean dysmenorrhoea numerical rating scale scores for people having relugolix CT. This was maintained at week 104 (84% reduction in dysmenorrhoea pain scores from baseline). The decrease in mean non-menstrual pelvic pain was also maintained. At week 52, there was a 63.5% decrease from baseline in mean non-menstrual pelvic pain for people having relugolix CT (with a reduction in pain from moderate to mild). This was maintained at week 104 (68.9% decrease from baseline). The committee concluded that, based on the

direct comparative evidence, relugolix CT was 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 indirect comparison showed no differences between relugolix CT and leuprorelin acetate in total pelvic pain (odds ratio [OR] 2.5, 95% credible interval [CrI] 0.032 to 190). The relative effect from an analysis on overall pelvic pain was used in the model to derive response rates for GnRH agonists. At consultation, the company did an updated indirect treatment comparison for overall pelvic pain and total pelvic pain. The studies included in the network for overall pelvic pain did not change from those included in the original indirect treatment comparison. They showed no differences between relugolix CT and leuprorelin acetate in overall pelvic pain (OR 0.99, 95% CrI 0.52 to 1.81, p=0.422). The mean difference between relugolix CT and leuprorelin acetate results were similar between the company's updated response (mean difference -0.02, 95% CrI -0.72 to 0.66) and those originally presented (mean difference 0.070, 95% CrI -0.61 to 0.74). The updated results for total pelvic pain found a greater effect of leuprorelin compared with relugolix CT (OR 1.35, 95% CrI 0.95 to 1.74, p<0.001). It also showed a greater advantage to leuprorelin acetate in the updated indirect treatment comparison (mean difference 1.35, 95% CrI 0.95 to 1.74) compared with those originally presented (mean difference 0.56, 95% CrI 0.017 to 1.1). The company explained the inconsistency was because of the way in which the pain scores were gathered. Overall pelvic pain was reported using the numeric rating scale (NRS), and total pelvic pain using the Biberoglu and Behrman scale that combined pain symptoms into scores. The company explained only the NRS has published minimal clinically important differences. The company provided evidence to show similar efficacy of relugolix in other disease areas. This showed non-inferiority of relugolix alone (without estradiol and norethisterone) compared with GnRH agonists in reducing endometriosis-associated pelvic pain and dysmenorrhoea, and in reducing heavy bleeding associated with uterine leiomyomas (fibroids). The committee

concluded that an indirect comparison was appropriate in the absence of direct head-to-head trials. It acknowledged the results of the indirect treatment comparison were uncertain and did not include a comparison of relugolix CT with surgery. But it was satisfied that the company's updated indirect treatment comparison had shown the relative effectiveness of relugolix CT compared with GnRH agonists.

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 have response to treatment switched to best 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. At consultation, the company stated the current model structure did reflect the treatment pathway because it spanned a lifetime horizon and captured the options available after stopping treatment with relugolix CT or GnRH agonists. It explained a proportion of people may have surgery after stopping relugolix CT and the model captured that some people may choose a more radical surgery, such as a hysterectomy. The model also captured pain recurrence after surgery. This was to reflect that not everyone has complete response to surgery and may have subsequent treatment, either with best supportive care or additional surgeries. The company noted its economic model had the functionality to compare relugolix CT with surgery. Surgery as a comparator was implemented in the same way as surgery as a follow-up treatment after relugolix CT or GnRH agonists, except during the first model cycle. This analysis suggested relugolix CT was more effective but more costly than surgery. The EAG was uncertain whether second-line inputs for surgery could be generalised to first-line inputs because the efficacy inputs for surgery had not been informed by the indirect treatment comparison that informs the relugolix CT and GnRH agonist arms (see section 3.10). But the EAG noted the

model was relatively robust to changes to input parameters, so applying different efficacy data would have a minimal impact on the cost-effectiveness results. The committee noted that the model had been developed at a global level, so there were some parameters that might not apply directly to the UK. It acknowledged it had not seen the relative efficacy data to inform surgery as a first-line treatment option. But it decided the model appropriately captured the treatment pathway and was appropriate for decision making.

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 decided that more clarity was needed on how best supportive care is defined and modelled. At consultation, the company clarified that best supportive care after relugolix CT would likely to be analgesics for pain management, although surgery may be an option for some people. It clarified that hormonal treatments would not be part of best supportive care at this point in the pathway because people will already have had hormonal therapies. The EAG was concerned that the efficacy of best supportive care treatments would not be estimated for the appropriate population, because the model had not been updated with additional comparator treatments. The committee noted that the model appeared to be robust to changes in efficacy (see section 3.11). It concluded it was satisfied that the appropriate treatments for best supportive care had been included.

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. At the first committee meeting, the committee recalled that GnRH

agonists are licensed for 6 months but are used longer in clinical practice (see section 3.3). 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 use 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 3.3). 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. At the first meeting, the committee concluded that it would prefer to see sensitivity analysis using longer treatment durations for GnRH agonists to reflect variations in clinical practice. At consultation, the company provided scenarios including GnRH agonists being used for up to 5, 7 and 10 years. In each scenario, relugolix CT was less costly but more effective than GnRH agonists. The EAG explained that as the treatment duration for GnRH agonists increases, the costs and quality-adjusted life years (QALYs) for GnRH agonists increase. So, the longer GnRH agonists are taken the more effective they are. In the company's base case, it would take 15 years (60 treatment cycles) of treatment with GnRH agonists to become more effective than relugolix CT. A scenario analysis exploring this showed that at 15 years, relugolix CT becomes less costly and less effective than GnRH agonists. The patient expert explained that although the duration of GnRH agonist use in clinical practice can vary, it is becoming more common for people to have treatment for 2 years or more. Different factors such as waiting time for surgery, results of bone density scans, and additional use of add-back therapy can influence how long these are used for. The clinical expert also explained that in their practice, some people might use GnRH agonists for up to 6 years. The committee noted that the company's scenario analyses, varying the duration of GnRH agonist use, had shown consistent results up to 10 years. Because the durations of GnRH agonist use can vary, it concluded that the duration of 1 year (applied in the company's base case) was appropriate.

Clinical outcomes used in the model

3.14 The model used the co-primary endpoints from the SPIRIT trials (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 advised 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 it would like to have seen more dimensions that are important to patients' quality of life and costs included in the model.

Treatment effect waning and discontinuation

3.15 In the company's base case, people took relugolix CT until they did not have 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. At consultation, the company stated it did not anticipate any waning of treatment effect with relugolix CT. Data from the SPIRIT open label extension study suggested that treatment response was maintained over 2 years of relugolix CT treatment (see section 3.9). The company noted there was no increase in the discontinuation rate because of lack of efficacy between SPIRIT 1 and 2 and the open label extension study. The maximum discontinuation rate from the SPIRIT trials was 0.033. So, the company did a 'pessimistic scenario' in which this discontinuation rate was applied at 21 and 24 months. It also did an 'optimistic scenario' in which the minimum discontinuation rate (0) was applied at 21 and 24 months. Both of these scenarios had little impact on the cost-effectiveness results. The EAG advised that a better way to capture treatment effect waning would have been to adjust the response rates over time. It had not explored this, because there was no data to inform the response rates over time. But because the model was relatively stable it advised this would have a minor impact on the results. The committee noted there was limited long-term evidence and no direct indication on whether it is biologically plausible that the treatment effect of relugolix CT would wane over time. But it was satisfied that the company had provided the best evidence it had to inform follow-up. It decided any loss of treatment effect could be captured in the discontinuation rates included in the company's base case. The company's model had incorporated discontinuation rates over time applied at each model cycle (every 3 months). These varied from 0.017 at 3 and 6 months, 0.033 at 9 months, 0.021 at 12 months and 0.012 at 15 months or above. The committee noted that the company's scenario analyses had used the highest discontinuation rate (0.033, observed at 9 months) and applied this to 21 and 24 months. This had a limited impact on the cost-effectiveness results. It

accepted that the discontinuation rates applied in the company's base case was appropriate.

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 company explained the results were not counterintuitive and were caused by the restriction on treatment duration for GnRH agonists. The committee recognised the impact that stopping GnRH agonist use could have in the model. It was satisfied that the counterintuitive results had been explained and were likely caused by discontinuation of GnRH agonists.

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 advised this is low and noted that it came from a very wide range reported in the literature (0.15 and 0.78). The company noted that the highest baseline value (0.78) was obtained in a population with less severe symptoms than in the SPIRIT trials. 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 first 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 'non-responders' had a high utility value. The clinical expert noted that there are aspects to pain other than its severity (for example, pain in the bladder, bowel, migraine, and chronic fatigue). The company suggested that people in the SPIRIT trials had access to analgesics. 'Non-responders' to relugolix CT may have had some benefit from the analgesics, which impacted on their utility scores. The committee decided there was uncertainty about the utility values used in the model. In response to consultation, the company explained the systematic literature review identified a utility value of 0.49 in a population that was aligned to the SPIRIT trial. The company also did a scenario analysis in which the utility of non-response was set to equal the baseline utility. This had a minor impact on the cost-effectiveness results. The EAG explained the total QALYs were relatively insensitive to single changes in utilities. The committee concluded that the company's baseline utility values were uncertain but plausible and suitable for decision making.

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. The company stated this would have a minimal impact on the results but the EAG disagreed. The EAG 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. But a multiplicative approach is usually preferred (section 4.3.7 of NICE's health technology evaluations manual). It stated that the company should justify its approach and explore the impact with scenario analyses. At consultation, the company stated it understood that a multiplicative approach is typically used for

an age-related decrement and an additive approach is used for other disutilities. It had not explored applying a multiplicative approach so the EAG was unable to validate the impact. But the EAG advised that applying a multiplicative approach was likely to have a minor impact on the cost-effectiveness results. The committee would have preferred to have seen the impact from a multiplicative approach to applying disutilities from adverse events. But in the absence of a multiplicative approach and noting the impact was likely small, it was satisfied that an additive approach could be used in the company's base case.

Disutility from infertility and hysterectomy

3.19 The company did not explicitly model the disutility from infertility related to having a contraceptive treatment. It stated that any differences in utility because of infertility between treatments would have been captured in the EQ-5D measurements in the trial. But the EAG advised the impact on infertility could be greater for people taking relugolix CT because the treatment was given for longer. It also noted 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 decided best supportive care and surgery were not feasible options for these people. The EAG 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). At consultation, the company stated this is not appropriate because it would assume that the disutility associated with a hysterectomy is only limited to infertility. But hysterectomy can have a substantial impact on quality of life beyond infertility. The company's base case assumed a short-term acute disutility of 0.054 and long-term disutility of 0.18 to all health states after hysterectomy. The EAG noted the long-term disutility value was taken from a global burden of disease report (World Health Organisation global burden of disease 2004 update, originally

published 1990). It was assumed to represent the disutility linked to infertility after removal of the uterus. For conservative surgery there was no long-term disutility because surgery would preserve the uterus, suggesting no long-term impact. The company explained this had been chosen as the most appropriate way to capture the disutility. At consultation the company provided scenario analyses varying the long-term disutility from hysterectomy from 0.1, 0.05 and 0.01. These results showed the lower the disutility the higher the incremental cost-effectiveness ratio (ICER) for relugolix CT compared with both GnRH agonists and surgery. The EAG found the company's approach to capturing disutility from infertility or hysterectomy (applying a single change in disutility to everyone) too simplistic, particularly because fertility drives treatment choice (in line with NG73). It noted that based on the model structure, disutility from infertility or hysterectomy had a big impact on the cost-effectiveness results. It did exploratory analyses, considering no disutility from hysterectomy or infertility, applying the utility decrements from hysterectomy and infertility to a proportion of people up to a certain age and including each disutility with surgery as a comparator. It noted that despite the company suggesting a utility decrement to hysterectomy should be applied, it had still applied the same decrement for infertility (0.18) within its base case. The company explained it used this value because it could not find a long-term disutility value specifically for hysterectomy. The committee acknowledged the uncertainty around how infertility and hysterectomy were incorporated into the model. It recognised that experiences of this disutility are diverse and dependent upon multiple factors, such as individual characteristics and experiences that are very difficult to capture in a single disutility for this parameter in the economic model. But it noted a value of 0.18 applied to everyone was a high disutility. It noted it is plausible that some people might have a high long-term disutility after hysterectomy; for example, because of infertility, significant complications or experiencing menopausal symptoms after an oophorectomy. But some people might not have any long-term disutility. The committee concluded that it would be reasonable to apply a lower disutility to all people in the model to capture this. It considered the company's scenario analyses and concluded that out of the scenarios provided, a disutility of 0.05 would be the most appropriate long-term disutility to apply to the full population.

Cost-effectiveness estimates

Company cost-effectiveness estimate

3.20 Because of confidential commercial arrangements for comparator treatments, the exact cost-effectiveness estimates are confidential and cannot be reported here. But the company's ICERs for relugolix CT compared with GnRH agonists were within what is normally considered a cost-effective use of NHS resources.

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. At the first meeting, the committee had been uncertain about the model inputs and cost-effectiveness estimates. At the second meeting, the committee was satisfied that the company had provided appropriate evidence and scenario analyses to resolve some of the uncertainties. But uncertainties remained about the:

- results of the indirect treatment comparison (see section 3.10)
- clinical outcomes used in the model (see section 3.14)
- utility values used in the model (see section 3.17)
- impact of applying a multiplicative approach to disutilities (see section 3.18)
- long-term disutility associated with hysterectomy (see section 3.19).

The committee decided an acceptable ICER would be around £20,000 per QALY gained.

Committee's preferred cost-effectiveness estimate

3.22 The committee's preferences for the cost-effectiveness modelling of relugolix CT were mostly aligned with the company's base-case assumptions. But the committee preferred to apply a long-term disutility of 0.05 for hysterectomy. It concluded that the most plausible ICER using its preferred assumptions was within the range considered a cost-effective use of NHS resources. The exact ICERs are confidential and cannot be reported here because of confidential discounts for technologies included in the modelling.

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.
- 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 advised that relugolix CT is a step-change in the management of endometriosis. This is 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 noted 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 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. Relugolix CT also has contraceptive properties. The summary of product characteristics notes that after at least 1 month using relugolix CT, it provides adequate contraception to those having the recommended dose. The committee concluded that there are additional benefits of relugolix CT for endometriosis that may not have been captured in the modelling.

Conclusion

Recommendation

3.25 The committee concluded that the most plausible ICERs were within the range considered a cost-effective use of resources. So, relugolix CT can be used, within its marketing authorisation, as an option for treating symptoms of endometriosis in adults who have had medical or surgical treatment for their endometriosis.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has endometriosis and the healthcare professional responsible for their care thinks that relugolix CT is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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 and Victoria Gillis-Elliott
Technical leads

Elizabeth Bell and Nigel Gumbleton
Technical advisers

Kate Moore
Project manager

Linda Landells and Janet Robertson
Associate directors

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