NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Relugolix–estradiol–norethisterone acetate for treating moderate to severe symptoms of uterine fibroids

1 Recommendations

1.1 Relugolix–estradiol–norethisterone acetate is recommended, within its marketing authorisation, as an option for treating moderate to severe symptoms of uterine fibroids in adults of reproductive age.

Why the committee made these recommendations

Treatment options for symptoms of uterine fibroids include levonorgestrel-releasing intrauterine system or combined hormonal contraception. But for treating moderate to severe symptoms of uterine fibroids, injectable gonadotrophin-releasing hormone (GnRH) agonists are often used before surgical options. Relugolix–estradiol–norethisterone acetate, taken orally, is another treatment option for moderate to severe symptoms of uterine fibroids.

Clinical trial evidence shows that relugolix–estradiol–norethisterone acetate is more effective than placebo for reducing heavy menstrual bleeding. It has only been indirectly compared with GnRH agonists and this suggests it is similarly effective to them, but the results are uncertain.

There are likely additional benefits of relugolix–estradiol–norethisterone acetate not captured in the economic model, including that it:

- is an effective non-surgical treatment
- is taken orally

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- can be used long term, which could mean improved and sustained symptom relief
- is well tolerated
- preserves the uterus and fertility.

So, despite the uncertainty in the clinical evidence, taking these benefits into account, the cost-effectiveness estimates for relugolix–estradiol–norethisterone acetate are likely within what NICE normally considers an acceptable use of NHS resources. It is therefore recommended.

2 Information about relugolix–estradiol–norethisterone acetate

Marketing authorisation indication

2.1 Relugolix–estradiol–norethisterone acetate (Ryeqo, Gedeon Richter UK) is indicated for the 'treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of relugolix–estradiol–norethisterone acetate is £72.00 for a 28-pack of 40 mg/1 mg/0.5 mg tablets (excluding VAT; BNF online, accessed April 2022). The annual treatment cost is £939.21. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee considered evidence submitted by Gedeon Richter UK, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Uterine fibroids can have substantial effects on quality of life

3.1 Uterine fibroids are non-cancerous growths (myomas or leiomyomas) that develop in or around the uterus. The exact cause is not known, but they have been linked to oestrogen, occur in people of reproductive age and can become smaller after menopause. Around 1 in 3 women develop uterine fibroids, and incidence increases with age until the menopause, with a peak in the 40s. Symptoms are broadly classed into prolonged and heavy menstrual bleeding, pelvic pain and pressure, and reproductive dysfunction. A patient organisation submission noted that the symptoms can significantly affect the careers and family lives of people with uterine fibroids, who typically manage them without any support. This is because there are limited long-term treatments options, recovery times after surgical interventions are prolonged, and some treatment options affect fertility and sexual function. The clinical experts explained that heavy menstrual bleeding from uterine fibroids can have a significant effect on the social and professional lives of people affected, and on finances. This can affect mental health and quality of life. The committee concluded that uterine fibroids represent a significant burden for people with them, affecting both physical and psychological aspects of quality of life.

Treatment pathway and comparator

There is an unmet need for effective treatments to manage symptoms of uterine fibroids and a new treatment option would be welcomed

3.2 A clinical expert submission at the technical engagement stage highlighted that the aim of treatment for uterine fibroids can vary. It can be to prevent disability due to anaemia or pressure, or for effect on fertility. Therefore, in clinical practice, treatment is determined based on clinical presentation, effect on quality of life, fertility desires and preferred treatment choice. The clinical experts highlighted that treatment for symptomatic uterine fibroids is generally aligned with NICE's guideline on

heavy menstrual bleeding: assessment and management. This recommends that, when there is no identified cause and fibroids are less than 3 cm in diameter, pharmacological treatments include non-hormonal (tranexamic acid, non-steroidal anti-inflammatories) and hormonal medicines (levonorgestrel intrauterine system, combined hormonal contraception, cyclical oral progestogens). If pharmacological treatment is unsuccessful or declined, or symptoms are severe, then surgical options (endometrial ablation, hysterectomy) are offered. When fibroids are 3 cm or more in diameter, uterine artery embolisation is another option before surgery. Ulipristal acetate (a hormonal medicine) and myomectomy (a surgical option) are only considered if other surgical options and uterine artery embolisation are unsuitable, declined or unsuccessful. Pretreatment with injectable gonadotropin-releasing hormone (GnRH) agonists before hysterectomy and myomectomy is considered if uterine fibroids are causing an enlarged or distorted uterus. The clinical experts explained that control of menstrual blood loss volume is a clinically important outcome because it reduces the risk of anaemia and improves quality of life. Both the patient organisation submission and the clinical experts explained the limitations of current treatments. These included short-term management before hospital treatment, unpleasant side effects with hormonal therapies, and the effect on fertility from some surgical procedures, such as hysterectomies and endometrial ablation. The clinical experts further highlighted the logistical challenges, resourcing needs and associated costs, and the inconvenience of having to attend clinics to have injectable GnRH agonists. Also, GnRH agonists are only licensed to be used for up to 6 months. The committee concluded that there is an unmet need for a licensed, long-term, non-invasive, safe and effective treatment to manage symptoms of uterine fibroids. It added that people with the condition and clinicians would welcome a new treatment option.

GnRH agonists are the most relevant comparators for relugolix–estradiol–norethisterone acetate

3.3 In its submission, the company compared relugolix–estradiol–norethisterone acetate with GnRH agonists. It considered that options such as levonorgestrel-releasing intrauterine system or combined hormonal contraception were not relevant options for treating moderate to severe symptoms of uterine fibroids. It stated that GnRH agonists would be the most relevant comparators expected to be displaced by relugolix–estradiol–norethisterone acetate for managing heavy menstrual bleeding. It highlighted that 3 of the GnRH antagonists identified in its systematic literature review (elagolix, linzagolix and cetrorelix) are not licensed for use in people with uterine fibroids. Therefore, they were not considered relevant comparators for this appraisal. It further explained that, because of safety concerns about liver injuries, ulipristal acetate is only indicated for intermittent treatment when uterine fibroid embolisation or surgery are unsuitable or unsuccessful. The company also asserted that the low usage of ulipristal acetate in clinical practice showed that GnRH agonists are the most relevant comparators for this appraisal. The ERG agreed that it was justifiable to exclude GnRH antagonists as comparators. It considered it unlikely that many people with uterine fibroids needing treatment would agree to have ulipristal acetate, given the level of monitoring needed and potential risks of liver damage. The company's submission assumed that all GnRH agonists are equally effective, and the evidence for GnRH agonists as a comparator was represented by clinical evidence for leuprorelin acetate. The clinical experts explained that the choice of GnRH agonists in clinical practice varies between NHS trusts. Some clinicians prefer leuprorelin because of the smaller needle size while others prefer goserelin. The committee considered that the company's positioning of relugolix reflected the place in therapy anticipated by the Europe Medicines Agency in the European Public Assessment Report. The committee therefore concluded that GnRH

agonists were the most appropriate comparators for relugolix–estradiol–norethisterone acetate.

Clinical-effectiveness evidence

Trial evidence from LIBERTY 1 and LIBERTY 2 suggests that relugolix–estradiol–norethisterone acetate is more effective than placebo

3.4 The clinical evidence for relugolix–estradiol–norethisterone acetate came from 2 identical phase 3 randomised controlled trials, LIBERTY 1 and LIBERTY 2. The trials compared relugolix–estradiol–norethisterone acetate (n=128 and n=126 respectively), relugolix with delayed oestradiol and norethisterone acetate (n=132 and n=127 respectively) and placebo (n=128 and n=129 respectively) for heavy menstrual bleeding associated with uterine fibroids. The key inclusion criteria in the trials were:

- being premenopausal
- age 18 to 50 years
- regular menstrual periods lasting less than 14 days
- a cycle of 21 to 38 days
- a diagnosis of fibroids confirmed with ultrasonography
- heavy menstrual bleeding (MBL; 160 ml or more during 1 cycle or 80 ml or more per cycle for 2 menstrual cycles) assessed by the alkaline haematin (AH) technique of measuring menstrual blood loss volume.

Planned surgery within 6 months of enrolment was an exclusion criterion in both trials. None of the data from the relugolix with delayed oestradiol and norethisterone acetate arms from the trials are considered in this appraisal. The primary outcome measure was a menstrual blood loss volume of less than 80 ml and at least a 50% reduction from baseline in menstrual blood loss volume over the previous 35 days of treatment. The results from the LIBERTY 1 and 2 showed that the primary outcome measure was reached by 73% and 71% respectively of people in the relugolix–estradiol–norethisterone acetate arms compared with 19% and

15% respectively in the placebo arms. Also, LIBERTY 3 (n=477), an open-label single-arm extension study of LIBERTY 1 and 2, provided long-term clinical evidence for relugolix–estradiol–norethisterone acetate. Evidence from all 3 trials was used to inform the economic model. However, only evidence from LIBERTY 1 and 2 was used to inform the indirect treatment comparison. The committee concluded that the results from LIBERTY 1 and 2 showed that relugolix–estradiol–norethisterone acetate is more effective than placebo for treating heavy menstrual bleeding associated with uterine fibroids.

The indirect treatment comparison is appropriate in the absence of head-to-head trials with GnRH agonists

3.5 There was no evidence directly comparing relugolix–estradiol–norethisterone acetate with GnRH agonists. Therefore, the company presented a separate indirect treatment comparison of relugolix–estradiol–norethisterone acetate (LIBERTY 1 and 2) compared with ulipristal acetate (PEARL 1) and a direct comparison of ulipristal acetate compared with leuprorelin, a GnRH agonist (PEARL 2). Menstrual blood loss volume was the only outcome reported in the results of the indirect and direct treatment comparisons. The ERG considered that a network meta-analysis would have been a more appropriate form of analysis. This was because it would better represent the uncertainty because of the number of comparisons needed and the imbalances in the baseline characteristics between PEARL 1 and the LIBERTY and PEARL 2 trials. At technical engagement, the company highlighted that a network meta-analysis would not have been more informative, and that their method was more transparent. It explained that the model used menstrual blood loss volume at 14 different timepoints and converted the values to utility. Therefore, a network meta-analysis of these timepoints would have been needed to provide inputs for the economic model. The committee questioned whether the company could have done an anchored matching adjusted indirect comparison using patient-level data from the LIBERTY and PEARL trials to better characterise this uncertainty. The company

highlighted that it did not have access to the required patient-level data to do this. It explained that it considered the differences in baseline characteristics were not treatment-effect modifiers. This was because the subgroup analysis at the technical engagement stage showed no differences in menstrual blood loss volume. The committee was concerned that the most robust methods to characterise uncertainty in the comparative effectiveness of relugolix–estradiol–norethisterone acetate compared with GnRH agonists may not have been used. However, it concluded that an indirect comparison was appropriate in the absence of head-to-head trials with GnRH agonists.

Menstrual blood loss volume is a relevant outcome measure of treatment effectiveness for uterine fibroids

3.6 Heavy menstrual bleeding is defined as greater than 80 ml or more menstrual blood loss volume. Assessing menstrual blood loss volume using the AH technique by chemically measuring the blood content of used sanitary products is considered the 'gold standard'. Other validated tools include Pictorial Blood Loss Assessment Charts (PBACs), which offers a semi-objective method for evaluating heavy menstrual bleeding. A PBAC score of more than 100 points correlates with a menstrual blood loss volume of 80 ml or more. The committee was concerned that 2 different methods for measuring menstrual blood loss volume were used in the LIBERTY and PEARL trials (AH technique and PBAC respectively). This may have meant that the treatment effect was not comparable across trials. One clinical expert highlighted that the AH technique is a more accurate measurement of menstrual blood loss volume. Another clinical expert highlighted that the perception of improvement in symptoms and quality of life associated with reduced menstrual blood loss is also important. However, this is subjective. That is, 1 person may have a higher menstrual blood loss volume but be able to cope with their condition better than another who has lower menstrual blood loss volume, depending on how it affects their lives. Although the AH technique is the more accurate of the 2 methods, the PBAC score may more accurately

reflect the subjective experience associated with menstrual bleeding. The clinical expert further explained that because the LIBERTY and PEARL trials both measured menstrual blood loss volume, the trials should be considered comparable. Menstrual blood loss volume was the only outcome used to assess the comparative efficacy of relugolix–estradiol–norethisterone acetate compared with GnRH agonists. The ERG report noted concerns with using menstrual blood loss volume as the only outcome for which the company did an indirect treatment comparison. Uterine fibroid volume, haemoglobin levels and health-related quality of life were reported in the LIBERTY and PEARL trials. Also, time to menstrual blood loss response and pain were listed in both the NICE final scope and company's decision problem. Any of these outcomes could have been assessed using an indirect treatment comparison. However, the company's technical engagement response highlighted that doing indirect treatment comparisons of other outcomes were not feasible. The clinical experts explained that amenorrhoea is the principal aim when treating heavy menstrual bleeding associated with uterine fibroids and reducing menstrual blood loss volume is an important outcome. They explained that menorrhagia has a significant effect on quality of life. Although, reducing fibroid size may be an important clinical outcome, it is the reduction in menstrual blood loss volume that people with uterine fibroids value more. The committee was aware that other relevant outcomes could have been assessed in the indirect treatment comparison to determine the comparative effectiveness of relugolix–estradiol–norethisterone acetate and GnRH agonists more robustly. However, it concluded that menstrual blood loss volume was a relevant outcome to measure the effectiveness of treatments for uterine fibroids.

Relugolix–estradiol–norethisterone acetate is likely to be as equally effective as GnRH agonists

3.7 The results of the company's indirect treatment comparison suggested that relugolix–estradiol–norethisterone acetate is at least equally effective as GnRH agonists. The mean differences in percentage change from

baseline in menstrual blood loss volume between relugolix–estradiol–norethisterone acetate and leuprorelin were:

- at week 4, -50.6 ml (95% confidence interval [CI] -141.6 ml to 40.4 ml)
- at week 8, 8.3 ml (95% CI -96.5 ml to 113.1 ml)
- at week 12, -9.2 ml (95% CI -84.5 ml to 66.0 ml).

The ERG agreed that the results suggested relugolix–estradiol–norethisterone acetate and GnRH agonists were equally effective in reducing menstrual blood loss volume from heavy menstrual bleeding associated with uterine fibroids. However, it highlighted that the wide confidence intervals suggested substantial uncertainty, which should have been represented in the probabilistic sensitivity analysis. The committee noted the large differences in baseline menstrual blood loss volume between the pooled data from LIBERTY 1 and 2 and PEARL 1 and 2. It questioned the increase in menstrual blood loss volume from baseline to week 4 for leuprorelin and from week 8 to week 12 for both ulipristal acetate and leuprorelin in PEARL 2. The clinical experts explained that, because of the mechanism of action of GnRH agonists an initial increase in menstrual blood loss volume would be expected in the first couple of months. They added that this is often discussed with patients before starting treatment. They further highlighted that, in PEARL 2, add-back therapies were not included and noted that such therapies may reduce the efficacy of GnRH agonists. The committee remained concerned that the results of the indirect treatment comparison were highly uncertain. It considered that the evidence presented did not clearly show a difference in treatment effect. However, it cautiously accepted that the treatment effect for relugolix–estradiol–norethisterone acetate was not any worse than for GnRH agonists. The committee concluded that, despite the uncertainty in the indirect treatment comparisons, relugolix–estradiol–norethisterone acetate is likely to be as equally effective as GnRH agonists.

Relugolix–estradiol–norethisterone acetate is likely to be used in NHS clinical practice irrespective of whether the surgery is planned or not

3.8 The ERG report noted that the population assessed in the LIBERTY trials did not match that assessed in the PEARL trials. In the PEARL trials, everyone had surgery planned after 13 weeks. For the LIBERTY trials, planned surgery within 6 months of enrolment was an exclusion criterion. The ERG also considered that relugolix–estradiol–norethisterone acetate may be used in clinical practice as a 'presurgery' treatment. This would be more consistent with the population in PEARL 2 than the population in the LIBERTY trials. Surgery rates were not collected in the LIBERTY trials. As such, in the economic model, monthly probabilities of transition to surgery for people having relugolix–estradiol–norethisterone acetate were based on data from PEARL 2 for GnRH agonists. The ERG suggested that analysis in the 2 populations (that is, no planned surgery or planned surgery including people planning to have surgery) may have been more appropriate. At technical engagement, the company highlighted that relugolix–estradiol–norethisterone acetate is not restricted to presurgical use. Rather, it is a longer-term treatment option for people wishing to delay or avoid surgery. It also highlighted that GnRH agonists are not used solely as a preoperative treatment. In PERAL 2, 54.9% of people did not have surgery and transferred to best supportive care. The clinical experts noted that surgery was an exclusion criterion in the LIBERTY trials. However, they highlighted that relugolix–estradiol–norethisterone acetate is expected to be used longer term for people who cannot or choose not to have surgery, and also in the presurgical setting. This is because surgery is the main option for most people with heavy menstrual bleeding associated with uterine fibroids. The committee noted the paucity of clinical evidence for short-term use of relugolix–estradiol–norethisterone acetate in the presurgical setting. However, it concluded that relugolix–estradiol–norethisterone acetate is likely to be used in the NHS clinical practice irrespective of whether the surgery is planned or not.

Adverse events

Relugolix–estradiol–norethisterone acetate is generally well tolerated

3.9 The adverse event profile of relugolix–estradiol–norethisterone acetate for treating uterine fibroids in the company submission was informed by evidence from the LIBERTY trials. In LIBERTY 1, 62% of people who had relugolix–estradiol–norethisterone acetate had adverse events compared with 66% who had placebo. In LIBERTY 2, 60% of people who had relugolix–estradiol–norethisterone acetate had adverse events compared with 59% who had placebo. The most frequently reported adverse events in any treatment group included headache and hot flushes. Compared with placebo, vasomotor symptoms (most frequently hot flushes) were more common with relugolix–estradiol–norethisterone acetate (14 [11%] compared with 10 [8%] in LIBERTY 1, and 7 [6%] compared with 5 [6%] in LIBERTY 2). The hot flush events were reported mostly to be grade 1 or 2 in severity. No deaths were reported across both trials. Least-squares mean percent changes from baseline in bone mineral density in the Relugolix–estradiol–norethisterone acetate arm compared with placebo at week 24 were -0.356% compared with 0.052% respectively in LIBERTY 1 and -0.126% compared with 0.315% respectively in LIBERTY 2. There were no statistically significant difference seen between the groups. Serious adverse events in LIBERTY 1 were reported for 7 people (5.5%) in the relugolix–estradiol–norethisterone acetate arm and for 2 people (1.6%) in the placebo arm. In the relugolix–estradiol–norethisterone acetate arm, 2 serious adverse events were related to expulsion or prolapse of uterine fibroid. One of these events was assessed as being related to study drugs. In LIBERTY 2, serious adverse events were reported for 1 person (0.8%) in the relugolix–estradiol–norethisterone acetate arm and for 4 people (3.1%) in the placebo arm. None of them were considered to be related to the study drug. The incidence and distribution of adverse events between the LIBERTY 1 and 2 and the open-label extension study, LIBERTY 3, were generally similar, with no

unexpected safety issues. The ERG did not highlight any concerns with any differences in serious adverse events or rates of adverse events. The committee concluded that relugolix–estradiol–norethisterone acetate is generally well tolerated.

Economic model

The model structure using treatment states rather than health states may not adequately capture all health outcomes

3.10 The company presented a Markov model with mutually exclusive 'treatment' states informed by treatment-discontinuation assumptions to capture cost and quality-adjusted life year (QALY) implications. It used a lifetime horizon and a cycle length of 1 month.. The ERG highlighted that modelling 'treatment' states rather than states defined by 'health' outcomes was unconventional and that this approach was not fully justified by the company. It considered that health states (for example, mild, moderate and severe bleeding) or symptom control (controlled, uncontrolled) would have been more appropriate to capture health and quality-of-life benefits. This approach would have allowed menstrual blood loss volume data from the LIBERTY and PEARL 2 trials to be linked directly to treatment used. Also, in clinical practice, management of uterine fibroids is likely to be based on clinical need, determined by symptom control, and not necessarily treatment status (on or off). At technical engagement, the company highlighted that the use of treatment states was based on the approach reported in a peer-reviewed publication by Geale et al. (2017) for ulipristal acetate. It explained that consistent response criteria were not available in the LIBERTY and PEARL trials to allocate people to health states. It further highlighted that the treatment-state approach allowed best use of the limited available data, comparisons with other treatments and modelling of treatment discontinuation based on trial data. The committee considered that the company's use of treatment states rather than health states in the

economic model may not have adequately captured all health outcomes associated with different treatment options. However, it concluded that the model was broadly appropriate for decision making.

The discontinuation rates used in the economic model are highly uncertain

3.11 In its economic model, the company used discontinuation rates for relugolix–estradiol–norethisterone acetate from the LIBERTY trials, which were modified based on clinical expert opinion. For GnRH agonists, these were from PEARL 2. The ERG highlighted that modifying discontinuation rates from LIBERTY trials' data based on clinical expert opinion was subjective. It thought that using data directly from the trials would have been more reliable, ensuring consistency between modelled costs and treatment benefits for relugolix–estradiol–norethisterone acetate. The ERG acknowledged that PEARL 2 only provided discontinuation data for 3 months compared with 24 months of data from the LIBERTY trials. However, in the absence of data for discontinuation rates for GnRH agonists over the longer term, the ERG considered it was appropriate to use the PEARL 2 data to get discontinuation rates for GnRH agonists for a longer period. The company's technical engagement response highlighted that the discontinuation rates showed good face validity. This was because the proportion of discontinuations in LIBERTY 1 and 2 (45%) were derived from patient choice. Also, they were potentially associated with the inconvenience of the AH collection method for measuring menstrual blood loss volume. However, the ERG considered that this implied that stopping treatment because of patient choice was excluded. Therefore, the discontinuation rates for relugolix–estradiol–norethisterone acetate may be substantially higher than those included in the company's economic model. The clinical experts explained that, before the COVID-19 pandemic, people prescribed GnRH agonists before surgery were happy to continue treatment for the licensed 6 months. This was particularly so if they did not have to wait too long for surgery. But the

clinical experts estimated that about 40% of people having GnRH agonists would stop treatment, for example, because of side effects. They explained that this has changed during the COVID-19 pandemic because of waiting lists and delays for surgical procedures. It has meant that people have had no choice but to continue GnRH agonists for longer than the licensed 6 months. Trade-offs have had to be made between the side effects and benefits associated with GnRH agonists and the effect of heavy menstrual bleeding associated with uterine fibroids on quality of life if not treated. The committee heard that people having GnRH agonists need to attend a clinic regularly for injections. This can become onerous, and people are more likely to stop treatment than if they were taking oral tablets. However, the committee questioned whether adherence would be also an issue with oral medication, for example, as seen in psychiatry and with oral contraception. One clinical expert explained that lifestyle can affect adherence with oral medicines. However, another noted that many people would prefer to take an effective oral medicine regularly than visit a hospital for clinics for an injection. The committee remained concerned that the discontinuation rates were not accurately captured in the company's economic analysis, concluding that the rates used in the economic model were highly uncertain.

The model likely underestimates the utility values informing the QALY gains with relugolix–estradiol–norethisterone acetate

3.12 The company's economic model included treatment-specific utility values informed by MBL from the relugolix–estradiol–norethisterone acetate and best supportive care arms of the LIBERTY studies and, for GnRH agonists, using an indirect treatment comparison with PEARL 2. Three measures of quality of life were included in the LIBERTY studies: EQ-5D-5L, uterine fibroid symptom and quality of life (UFS-QoL) and patient global assessment. In both LIBERTY studies, the improvement in the UFS-QoL score was statistically significantly greater with relugolix–estradiol–norethisterone acetate than with placebo. Because EQ-5D-5L

data was insufficiently captured in the trials, an unpublished mapping algorithm was used to transform disease-specific data from UFS-QoL to EQ-5D based utilities. This used an ordinary least-squares function including age and menstrual blood loss volume as covariates. However, the ERG noted that the company did not provide sufficient justification for the choice of regression model. Therefore, the ERG considered the repeated-measures model provided by the company in response to clarification more appropriate for estimating appropriate standard errors to include in the probabilistic analysis. The committee considered that there may be additional treatment benefits with relugolix–estradiol–norethisterone acetate that were not captured in the utility estimates used in the economic model to inform the QALY gains. These would likely have a positive effect on the quality of life of people with uterine fibroids, and included that it:

- is an effective non-surgical treatment
- is administered orally
- can be used long-term basis, which could mean improved and sustained symptom relief
- has good tolerability
- preserves the uterus and fertility.

The committee concluded that the model likely underestimated the utility values used to inform the QALY gains with relugolix–estradiol–norethisterone acetate.

Cost-effectiveness estimates

Relugolix–estradiol–norethisterone acetate is recommended for treating moderate to severe symptoms of uterine fibroids

3.13 The company's base case deterministic incremental cost-effectiveness ratio (ICER) for relugolix-estradiol-norethisterone acetate was less than £20,000 per QALY gained using the confidential price discounts. Because

of the uncertainties in the clinical evidence, the committee considered the scenario analysis in which the effectiveness of relugolix–estradiol–norethisterone acetate was equalised with GnRH agonists. Taking into account confidential prices for GnRH agonists, this resulted in a higher incremental cost for relugolix–estradiol–norethisterone acetate. There was a small QALY gain due to different discontinuation and adverse event rates, but an ICER compared with GnRH agonists above NICE's usual cost-effectiveness range. However, the committee considered that there were uncaptured QALY benefits for relugolix–estradiol–norethisterone acetate (see section 3.12). It was aware that it would only need a small increase in the QALYs for relugolix–estradiol–norethisterone acetate for the resulting ICER to represent a cost-effective use of NHS resources, even assuming equal effectiveness. Therefore, the committee concluded that relugolix–estradiol–norethisterone acetate is recommended for treating moderate to severe symptoms of uterine fibroids in adults of reproductive age.

Innovation

Relugolix–estradiol–norethisterone acetate is innovative

3.14 The company considered relugolix–estradiol–norethisterone acetate to be innovative. This was because it addresses a significant unmet need for an effective non-surgical treatment that can be taken orally and long term, is well tolerated and preserves the uterus and fertility. Uterine fibroids are associated with a substantial health and economic burden, and current treatment options are often inadequate. The company highlighted that clinical trial evidence showed a reduction in symptoms and incidence of adverse events, with evidence of sustained treatment effectiveness for 2 years. The clinical experts highlighted that the treatment would be a step change for managing heavy menstrual bleeding associated with uterine fibroids. It could save a substantial amount of time for people having treatment and for their clinicians compared with injectable GnRH

agonists. This could reduce financial consequences, particularly for people from lower socioeconomic groups. The clinical experts explained that there are several benefits with an oral treatment compared with current treatment options. These include convenience, potentially leading to improved adherence, maintaining fertility and providing long-term control of symptoms. The committee recalled that some of these benefits were not adequately captured in the economic analysis by the company (see section 3.12). But it acknowledged the benefits offered by relugolix–estradiol–norethisterone acetate as an additional treatment option for managing moderate to severe symptoms of uterine fibroids. The committee concluded that relugolix–estradiol–norethisterone acetate is an innovative treatment for moderate to severe symptoms of uterine fibroids.

Equalities considerations

Recommending relugolix–estradiol–norethisterone acetate would adequately address equalities concerns

3.15 During the scoping stage, it was highlighted that relugolix–estradiol–norethisterone acetate should be available to everyone with uterine fibroids who is eligible. This may include people who are trans or non-binary. The company submission highlighted that women with an African or Caribbean family background are 2 or 3 times more likely to develop uterine fibroids than white women. It also noted that they may be more opposed to surgery because of cultural beliefs. Some people may also decline surgery because of professional and family commitments. The clinical experts highlighted that clinic visits for treatment with GnRH agonists can result in significant financial and time costs. This could be a particular problem for people from lower socioeconomic groups and may increase the 'did not attend' rate at clinics. During the committee meeting, 1 clinical expert highlighted the need for a more effective non-surgical treatment option for people not wanting to have a hysterectomy. The patient organisation submission noted the need for 'equality of esteem'

with ‘men’s’ conditions. For example, prostatectomies are rare unless there is progressive cancer. But removal of the uterus and other reproductive organs is common and often the only option because of a lack of other treatment choices. The committee acknowledged the equality concerns raised. It recognised that non-surgical interventions, such as relugolix–estradiol–norethisterone acetate, may provide a more suitable treatment option than surgery for uterine fibroids. In particular, it considered that the recommendations will provide the benefit of another treatment option when surgery has been declined. No other potential equalities issues were raised.

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 clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months 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 recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

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 uterine fibroids and the doctor responsible for their care thinks that relugolix–estradiol–norethisterone acetate is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
April 2022

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

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

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

NICE project team

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

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