

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final draft guidance

**Linzagolix for treating moderate to severe
symptoms of uterine fibroids**

1 Recommendations

1.1 Linzagolix is recommended as an option for treating moderate to severe symptoms of uterine fibroids in adults of reproductive age only if:

- it is intended to be used for longer-term treatment (normally for more than 6 months and not for people who need short term treatment, for example, before planned surgery)
- the following dosage is used:
 - with hormonal add-back therapy (ABT): 200 mg once daily
 - without hormonal ABT: 200 mg once daily for 6 months, then 100 mg once daily.

1.2 This recommendation is not intended to affect treatment with linzagolix 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

Usual treatment for moderate to severe symptoms of uterine fibroids includes hormonal contraceptives and gonadotropin-releasing hormone (GnRH) receptor agonists and antagonists. GnRH antagonists, such as relugolix combination therapy

(CT), may contain hormonal ABT. Other treatments include best-supportive care, for example iron supplements and painkillers.

Clinical trial evidence shows that linzagolix works better than placebo at treating moderate to severe symptoms of uterine fibroids. It has not been compared with relugolix CT in a clinical trial. Indirect treatment comparisons of linzagolix compared with relugolix CT are highly uncertain.

Even when taking this uncertainty into account, linzagolix with or without hormonal ABT is cost effective, but only when it is intended to be used for longer-term treatment (normally more than 6 months). It is not recommended for people who need short term treatment, for example, before planned surgery. The economic analysis for short-term use did not compare linzagolix against all relevant comparators, so the committee was unable to determine whether linzagolix was cost-effective in this population. So, it is only recommended for longer-term use.

2 Information about linzagolix

Marketing authorisation indication

2.1 Linzagolix (Yselty, Theramex) 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 for linzagolix](#).

Price

2.3 The list price of linzagolix is £80 for a 28 pack of 100 mg or 200 mg tablets. The cost for an 84 pack of estradiol and norethisterone tablets known as hormonal add-back therapy (ABT) is £13.20. At list price, 12 months of treatment would cost £1,040 (without ABT) and £1,097.20 (with ABT).

3 Committee discussion

The [evaluation committee](#) considered evidence submitted by Theramex, 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

Uterine fibroids effects on quality of life

3.1 Uterine fibroids are non-cancerous growths that develop in or around the uterus. Uterine fibroids occur in people of reproductive age and can become smaller after menopause. Their exact cause is not known, but they have been linked to oestrogen and progesterone. Around 66% of women develop at least 1 uterine fibroid during their lifetime and 33% of women will develop symptoms from uterine fibroids. Risk factors for developing uterine fibroids include age up to menopause, family history, not having given birth and Black African ethnicity. Moderate to severe symptoms of uterine fibroids include pain, difficulty in conceiving and heavy menstrual bleeding (HMB), which may lead to anaemia. A clinical expert noted that these symptoms can substantially affect the personal and professional lives of people with uterine fibroids. This may result in the breakdown of relationships and missed career opportunities which can further affect mental health and quality of life. The committee understood that moderate to severe symptoms of uterine fibroids have a substantial effect on quality of life.

Clinical management

Treatment pathway

3.2 The treatment pathway for moderate to severe symptoms of uterine fibroids differs depending on treatment aims and patient characteristics. Treatment for symptomatic uterine fibroids is generally aligned with [NICE's guideline on heavy menstrual bleeding: assessment and management](#). People initially have pain management and oral contraceptives to reduce the symptoms of uterine fibroids. Subsequent

treatment may include gonadotropin releasing hormone (GnRH) analogues which consist of:

- GnRH agonists such as leuprorelin, goserelin and triptorelin, which initially overstimulate gonadotropin releasing hormone receptors and later downregulate oestrogen and progesterone
- GnRH antagonists such as relugolix combination therapy (CT). These drugs bind and inhibit the GnRH receptor to downregulate oestrogen and progesterone.

As GnRH antagonists can result in very low oestrogen and progesterone levels, hormonal add-back therapy (ABT) may be used to reduce any adverse effects of these low levels (including low bone mineral density). This is the case with relugolix CT where hormonal ABT (estradiol–norethisterone acetate) is part of the treatment. Many people are offered surgery or interventional procedures to remove or reduce the size of uterine fibroids. Surgery may include myomectomy or hysterectomy and could be laparoscopic, hysteroscopic or open abdominal surgery. Interventional procedures may include uterine arterial embolisation, endometrial ablation and MRI-guided focused ultrasound. The treatments which are offered may depend on the specific treatment aims, patient characteristics (for example comorbidities) and personal preference, which may be not to have hormonal treatments. The clinical experts explained that one of the benefits of linzagolix is the flexible dosing and the potential to use either dose with or without hormonal ABT. The company proposed that the population could be split into 3 subgroups based on the duration of treatment and the requirement for hormonal ABT.

People having short-term treatment

3.3 A substantial number of people would have short-term treatment (usually 6 months or less) of linzagolix without hormonal ABT. This is often before uterine fibroid surgery with the aim of reducing fibroid size and improving

symptoms and surgical outcomes. This population will be referred to as the 'short-term usage population'. People in this population might currently have GnRH agonists or may have relugolix CT. Treatment would usually be followed by surgery or an interventional procedure. The clinical experts noted that for the short-term usage population, waiting times meant that people might be waiting longer than 6 months before surgery. The company positioned linzagolix in this population as an alternative to GnRH agonists and relugolix CT. The committee considered that this population was relevant to NHS clinical practice and concluded that GnRH agonists and relugolix CT were appropriate comparators.

- 3.4 In the company's original submission an indirect treatment comparison with GnRH agonists and relugolix CT was provided to support a cost comparison of linzagolix with relugolix CT (see section 3.13). The company later provided a cost utility analysis of linzagolix compared with relugolix CT at the request of the committee. The company excluded GnRH agonists from this analysis. It stated that this was because [NICE's technology appraisal TA832 on relugolix CT-estradiol-norethisterone acetate for treating moderate to severe symptoms of uterine fibroids](#) had concluded that relugolix CT and GnRH agonists were similarly effective. The committee did not agree with the company's justification, and considered that GnRH agonists should have been included as a comparator because people in this population currently have either GnRH agonists or relugolix CT. It further concluded that the exclusion of GnRH agonists from the analysis meant that it was not appropriate for decision making in this population.

People having longer-term treatment with hormonal ABT

- 3.5 People who need treatment for longer than 6 months may be offered relugolix CT (which contains hormonal ABT, see section 3.2). This population will be referred to as the 'longer-term with hormonal ABT population'. People in this population are likely to have had initial treatment consisting of a levonorgestrel intrauterine system, the combined hormonal contraceptive, or cyclical oral progestogens. They may then

have relugolix CT as a subsequent treatment. The clinical experts confirmed that people in the longer-term with hormonal ABT population would likely include people whose symptoms were not severe enough to warrant surgery and people who wanted to delay or avoid surgery because of the risks or for personal reasons, such as wanting to conceive. The company positioned linzagolix as an alternative to relugolix CT in this population. The committee noted that the marketing authorisation for linzagolix permitted its use as a longer-term option and considered that this population was relevant to NHS clinical practice and that relugolix CT was the appropriate comparator.

- 3.6 The company's original submission presented an indirect treatment comparison to support a cost-comparison analysis for linzagolix with relugolix CT in the longer-term with hormonal ABT population (see section 3.12). The company considered that as linzagolix and relugolix CT had a similar mechanism of action (see section 3.2) it was likely that they had similar clinical effectiveness and submitted evidence to support this consideration. A cost-comparison analysis also requires a comparator intervention that has been recommended by a NICE technology appraisal and is established in NHS practice in England with substantial use. The EAG clinical expert was unsure whether relugolix CT could be considered established practice as it had a relatively low uptake. The clinical experts noted that relugolix CT was recommended shortly after the withdrawal and subsequent reintroduction of ulipristal acetate for treating symptoms of uterine fibroids. This has delayed the uptake of relugolix CT, which has only been added to hospital formularies for about a year. They expected relugolix CT's uptake to be higher given its health benefits although its usage in clinical practice is increasing. The clinical experts noted that in their experience many people are more likely to have relugolix CT compared to GnRH agonists as it is an orally administered drug that does not need regular hospital visits. The committee concluded that it was reasonable to consider that relugolix CT was sufficiently part of established clinical practice to be considered a relevant comparator. It

noted that GnRH agonists are normally used short-term, so are not a relevant comparator for longer-term use. The company later provided a cost–utility analysis of linzagolix compared with relugolix CT at the request of the committee. The committee further concluded that a cost-utility comparison of linzagolix with relugolix CT was appropriate.

People having longer-term treatment without hormonal ABT

3.7 Some people who cannot or do not want to have hormonal therapy need longer treatment. This population will be referred to as the ‘longer-term without hormonal ABT population’. This population would have best-supportive care (BSC) which could include tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs) and iron supplements. The clinical experts considered that this population includes people for whom surgery presents unacceptable risks because of comorbidities or an elevated risk of blood clots. It also includes people who cannot have hormonal therapy for medical reasons such as having hormone sensitive breast cancer, and those who do not want it for personal reasons. The clinical experts noted that while this population was probably small, it was clinically important as they would not have other available treatment options and would benefit from a new treatment option. In its original evidence submission the company submitted a cost-utility analysis to compare linzagolix with BSC. The committee noted that the marketing authorisation for linzagolix permitted its use as a longer-term treatment option and concluded that this population was relevant to NHS clinical practice and that BSC was the appropriate comparator.

Clinical effectiveness

PRIMROSE 1 and 2 trials

3.8 The clinical evidence for linzagolix came from 2 randomised controlled trials, PRIMROSE 1 and 2, which compared linzagolix with placebo. The trials were very similar in structure, inclusion and exclusion criteria, and the outcomes measured. The company explained that because of the similarity of these trials, it was appropriate to give pooled efficacy data up

to week 24. The primary outcome for both trials was attainment of response, which was a reduction in HMB defined as menstrual blood loss (MBL) of less than or equal to 80 ml and a greater than or equal to 50% reduction in MBL from baseline. Secondary outcomes included percentage change from baseline in MBL, fibroid volume and uterine volume, pain, percentage change from baseline in haemoglobin in people with anaemia and change in quality of life (uterine fibroids severity and quality of life [UFS-QoL] and EQ-5D-5L instruments). Four different regimens of linzagolix and placebo were compared. The regimens assessed were 100 mg and 200 mg of linzagolix both with and without hormonal ABT. People having any linzagolix dosing regimen were significantly more likely to have a response than placebo. The greatest effect compared with placebo was seen with the 200 mg with hormonal ABT regimen, pooled analysis odds ratio (OR) 10.77 [95% confidence interval (CI) 6.66 to 17.42]. The 100 mg without hormonal ABT regimen had the lowest response effect compared with placebo, pooled analysis OR 2.75 [95%CI 1.82 to 4.16], and the remaining regimens, 100 mg plus hormonal ABT and 200 mg without hormonal ABT had results between these. The committee noted that there appeared to be a placebo effect for the response outcome as 66 people (32%) in the placebo group reported having a reduction in HMB in the pooled PRIMROSE results. The company explained that, in the PRIMROSE trials, MBL was measured using returned used sanitary products, and if no products were returned this was considered in the trial to mean there was no bleeding for that day. If people were unable to return sanitary products on the days of menstrual blood loss for any reason, then this may have overestimated the reduction in MBL. The company considered that the return of these products would be particularly burdensome in the placebo group, where there was heavier bleeding, and assume that this could have caused or contributed to the placebo effect. The EAG acknowledged this explanation but considered that it was speculative and that there could be other reasons for the placebo effect, such as regression to the mean. For the secondary outcomes, all linzagolix regimens were significantly better than

placebo with the exception of change from baseline in primary uterine fibroid volume and uterine volume outcomes for the 100 mg plus hormonal ABT regimen, and the EQ-5D-5L outcome. The committee noted that the 2 trials returned slightly different results with linzagolix appearing slightly more effective for some outcomes in PRIMROSE 2 than PRIMROSE 1. The EAG noted that this might reflect differences in the geographical and ethnic composition of the trial populations, but that this was uncertain. The committee concluded that linzagolix was more effective than placebo at treating moderate to severe symptoms of uterine fibroids.

Generalisability

3.9 The baseline characteristics of people in each PRIMROSE trial were similar between placebo and each of the linzagolix arms. But there were some differences in participant baseline characteristics between the trials. For example, 63% of people in PRIMROSE 1 were Black and 33% were White whereas the corresponding values for PRIMROSE 2 were 5% and 95%. In PRIMROSE 1 the mean weight and BMI were 88 kg and 32.7 kg respectively, with the corresponding values in PRIMROSE 2 being 74 kg and 27 kg. The EAG explained that both trials were generalisable and could be considered to represent clinical practice in different geographical locations in the UK. A clinical expert considered that the PRIMROSE trials were broadly representative of those who have severe uterine fibroid symptoms across NHS practice. The committee concluded that the baseline characteristics of the PRIMROSE trials were reflective of NHS clinical practice.

3.10 The EAG considered that the populations proposed by the company on which the economic analyses were based (see sections 3.3 to 3.7) were not explicitly represented in the PRIMROSE clinical trials. It noted that people with severe uterine fibroids who required urgent surgery within 6 months were excluded from the PRIMROSE trials, and that these people might be expected to make up a large proportion of the short-term usage population. The PRIMROSE trials also only had a follow up of 52 to 64

weeks (depending on the outcome), and the longer-term with hormonal ABT population was expected to include people who had linzagolix for over a year. Finally, the study excluded people who could not have hormonal ABT, which might be expected to make up a substantial proportion of the longer-term without hormonal ABT population. The company considered that those randomised to the linzagolix regimens without hormonal ABT would be a suitable proxy for those who did not have hormonal ABT in clinical practice. A clinical expert explained that they would not expect clinical responses to differ between those recruited to the PRIMROSE trials and the populations included in the economic analyses. The committee recalled that the marketing authorisation permitted linzagolix to be used as a longer-term treatment. It considered this and concluded that the PRIMROSE trials were sufficiently generalisable to the populations included in the economic analyses.

Adverse events

3.11 Incidence of adverse events in the PRIMROSE trials at week 24 was slightly higher across the linzagolix regimens compared with placebo but most adverse events were mild or moderate in severity. Serious and severe adverse events were broadly similar between the different arms of the PRIMROSE trials. There were fewer adverse events reported at week 52 than at week 24 and most adverse events reported at week 52 were mild to moderate in severity. There appeared to be a reduction in bone mineral density (BMD) during the first months of treatment with linzagolix and this was greater when the higher dose of linzagolix was used without hormonal ABT. At this higher dosage, the BMD reduction was not clinically meaningful (not a 5% or more reduction). The EAG commented that BMD loss during continued treatment after the first months was slower, but it was uncertain whether this pattern would be maintained in the longer-term. The committee were aware that for this reason the summary of product characteristics restricts the long-term use of linzagolix at the 200 mg dose without hormonal ABT to 6 months. The clinical expert submission noted that the publication of longer-term 2-year data for

relugolix CT (which has the same mechanism of action as linzagolix, see section 3.2) showed that there were no new adverse reactions up to 104 weeks. The committee acknowledged the adverse events associated with linzagolix and noted that they were represented in the cost-utility model.

Indirect treatment comparisons

3.12 As there was no evidence which compared linzagolix directly with relugolix CT or GnRH agonists, the company did indirect treatment comparisons for their analyses in the short-term and longer-term usage with hormonal ABT populations. Network meta-analyses (NMAs) and an anchored matching-adjusted indirect comparison (MAIC) were done to compare the 4 regimens of linzagolix against relugolix CT for the primary and secondary outcomes of the PRIMROSE trials. The company used the LIBERTY trials which had similar outcomes, trial structure and inclusion criteria to the PRIMROSE trials, and compared relugolix CT with placebo to inform the relugolix CT arms of the NMAs. The company submitted both fixed and random effects model NMAs when including the pooled PRIMROSE trial results, but for the separate PRIMROSE 1 and 2 trial results only submitted fixed effects model NMAs. The EAG preferred the random effects model NMAs for decision making as they considered them better suited to dealing with the heterogeneity between the PRIMROSE and LIBERTY trials but noted that it was wise to consider all possible analyses.

3.13 In its original evidence submission, the company submitted NMAs comparing linzagolix regimens with leuprorelin (which was used as a proxy for GnRH agonists). These analyses compared the results of the PRIMROSE trials with the results of the PEARL 1 and 2 trials. The PEARL 1 and 2 trials compared ulipristal acetate with placebo and with leuprorelin respectively, for the pre-operative treatment of symptomatic fibroids and its outcomes included pain, excessive bleeding, and fibroid size. NMAs were only possible for 3 outcomes which were response (reduction in HMB, see section 3.8), change in primary fibroid volume and change in haemoglobin from baseline in people with anaemia. The EAG considered

these analyses to be highly limited for several reasons. Firstly, the outcome of response was reported at both 13 and 24 weeks in the PEARL trials and it was not clear which outcome was used in the NMA. Secondly, the outcome of response was defined differently in the PRIMROSE trials, which used the alkaline haematin biochemical method to estimate MBL, and the PEARL trials, which used the pictorial blood assessment chart method (which involves visual inspection of used sanitary products). Finally, the network used in the NMA was not reported which made the assessment of the reliability of the analysis difficult. The EAG considered that these analyses were extremely limited and could not offer a useful estimate of the efficacy of linzagolix regimens compared with GnRH agonists. The committee considered the evidence and concluded that GnRH agonists are an important relevant comparator in the short-term usage population, but the company's original NMA comparisons with GnRH agonists were not appropriate for decision making.

3.14 The results of the NMAs are confidential and cannot be reported here but generally showed that for some outcomes, NMA models and dosing regimens linzagolix had favourable results against relugolix CT, while for others relugolix CT had favourable results. For most outcomes, dosing regimens and NMA models, no significant difference was detected between linzagolix and relugolix CT. The committee concluded at the first meeting that the NMAs did not show that linzagolix provided similar health benefits to relugolix CT so it would not be possible to conclude that linzagolix provides a cost-effective treatment option based on a cost-comparison analysis. The committee concluded that it would be necessary to see results of a cost-utility analysis, incorporating the various outcomes compared in the NMAs, to determine whether linzagolix was cost effective for the treatment of moderate to severe symptoms of uterine fibroids in the short-term usage and longer-term usage with hormonal ABT populations.

3.15 At consultation, the company provided updated NMAs to support cost-utility analyses for the short-term and longer-term usage with hormonal

ABT populations. Rather than using results from the NMAs, the company instead chose a naive comparison that used the linzagolix response rate from the pooled PRIMROSE trials and the relugolix CT response rate from the pooled LIBERTY trials for their economic analysis base case. The company explained that this was because the NMAs had substantial limitations. This included differences in how MBL outcomes were assessed and missing data was handled between the PRIMROSE and LIBERTY trials, as well as the presence of placebo effect heterogeneity across the trials, particularly for the primary MBL outcome. The NMAs also do not adjust for observed differences in the baseline characteristics of the included trials. The EAG agreed with the company about these fundamental limitations in the NMAs, but disagreed on the appropriateness of a naive comparison. The EAG explained that MAICs can be used to adjust for heterogeneity in the baseline characteristics of the included trials that NMAs do not adjust for, subject to the MAIC adequately matching the reference and comparator trial characteristics. It noted that the company's original anchored MAIC also does not specifically adjust for the difference in placebo effect between the trials, or account for the differences in the assessment of MBL between the PRIMROSE and LIBERTY trials. An unanchored MAIC could potentially account for at least part of the placebo effect if treatment effect modifiers responsible for the placebo effect are included in the matching, but it is unclear what these modifiers might be. The EAG further explained that while the company reported odds ratios with credible intervals in its NMAs, the credible intervals are not used in the economic analysis NMA scenarios, meaning that uncertainty in the response outcome is not considered. The EAG explored this uncertainty in its scenario analyses. The committee concluded that it would consider all indirect treatment comparisons in its decision making.

Economic model

Cost-utility analysis modelling approach

3.16 The company submitted a cost-utility state transition model to estimate the cost-effectiveness of linzagolix compared with relugolix CT and BSC. The model had 6 health states: controlled symptoms, uncontrolled symptoms, surgery and post-surgery, as well as a menopause state and an absorbing death state. People in the model transitioned from the controlled to uncontrolled health states based on the 24-week response outcome for linzagolix or placebo from the PRIMROSE trials (see section 3.8), and from the controlled to uncontrolled health states based on clinical opinion given to the company. The company assumed that 45.1% of people would have surgery (for consistency with [NICE's technology appraisal TA832 on relugolix CT-estradiol-norethisterone acetate for treating moderate to severe symptoms of uterine fibroids](#)) and this was converted into a per cycle probability of having surgery from the controlled or uncontrolled health states, which was the same for both arms of the model. The model assumed that once somebody had surgery, they would not experience any further symptoms. After consultation, the company also did an expert elicitation to reduce uncertainty around the types of surgery that people would be expected to have in each treatment arm. The estimated surgery distributions resulting from this elicitation were incorporated into the company's base case model for the short-term and longer-term usage with hormonal ABT populations. People in the model moved to the menopause state at 51 years and transitions to the death state were modelled using age-matched general population mortality rates. An additional procedure-related mortality risk was also applied to those who had surgery. The company submitted evidence for the 200 mg dose. The model assumed that everyone in the intervention arm that had 200 mg linzagolix without hormonal ABT had the 200 mg dose for 6 months and then 100 mg without linzagolix. This was intended to reflect the marketing authorisation which states that 200 mg linzagolix cannot be used for more than 6 months without hormonal ABT. Adverse events were modelled based on the incidence of anaemia, headache, hot flush, and nausea reported in the PRIMROSE trials. The committee concluded that it could only consider recommendations for the 200 mg dose of linzagolix as this

was the only dose presented in the company's economic model. It further concluded that the company's model structure was appropriate for decision making.

Post-surgery recurrence of fibroids and symptoms

3.17 The cost-utility model structure assumes that once people have surgery for uterine fibroids, they will not experience any further symptoms of uterine fibroids. The EAG considered that there was uncertainty around whether all types of surgery prevent recurrence of symptoms. A clinical expert submission explained that it was implausible to model no recurrence after all surgery types as fibroids can develop from a single muscle fibre within the uterus, and if the uterus is retained there is a chance for recurrence of both fibroids and symptoms. The clinical expert stated that the recurrence of fibroids and symptoms is complex and depends on many factors but that generally recurrence is more common after laparoscopic surgery than open surgery and is least common for hysteroscopic surgery. The only situation where there could be an expectation of zero recurrence is when people have a hysterectomy. The expert considered that roughly 5% to 10% of people having surgical interventions will need another intervention in 5 to 10 years. The committee acknowledged this and concluded that it was not appropriate to assume that there would be no recurrence of symptoms after all surgery types and would have preferred to see modelling of post-surgery recurrence that would better reflect NHS clinical practice. The committee concluded that while this was a source of uncertainty, it would be unlikely to affect the cost-effectiveness estimates because of the incidence and distribution of surgeries being modelled equally between arms in the model.

Utility values

Source of utility values

3.18 The PRIMROSE trials included both the UFS-QoL and the EQ-5D-5L scores as outcomes (see section 3.8). The company base case model

used the UFS-QoL scores mapped to the EQ-5D-3L as inputs to a regression model to estimate utility for the controlled and uncontrolled health states in the model. The company also provided a scenario which used the EQ-5D-5L scores mapped to the EQ-5D-3L to estimate health state utility values. The EAG noted that the NICE reference case prefers EQ-5D evidence to condition specific measures of quality of life and states that EQ-5D should be used when available, unless it is not appropriate. It also raised a concern around the methodology used to map the UFS-QoL results to the EQ-5D-3L as this used the symptom severity component of the UFS-QoL rather than the quality-of-life component. The company considered that the disease specific UFS-QoL was a more reliable measure of quality of life for people with symptoms of uterine fibroids which tend to vary during the menstrual cycle and tend to be more intense during menstruation. The company explained that the EQ-5D-5L has a recall period of 'today', meaning that if participants completed the instrument on a day when they were experiencing a lower intensity of symptoms, the instrument could substantially overestimate their quality of life. A clinical expert considered that the UFS-QoL was preferred to EQ-5D when assessing quality of life in relation to HMB because EQ-5D might not capture full effects on quality of life depending on when the instrument was used. They highlighted concerns with using the EQ-5D to capture quality of life in cyclical conditions such as HMB. The committee noted that the committee for TA832 accepted utilities informed by the UFS-QoL, although this was in the absence of sufficient EQ-5D-5L data. It noted that the EQ-5D had the potential to not capture the full effects on quality of life of symptoms of uterine fibroids and concluded that it was appropriate to use the UFS-QoL instrument to derive utility values for this cost-utility model.

Costs

Resource use

3.19 The company modelled healthcare resource use with estimates that were approved in TA832 and this included numbers of GP visits, DEXA scans,

blood counts and magnetic resonance imaging scans for both the linzagolix and comparator arms. The EAG consulted a clinical expert and used a slightly different distribution of the same healthcare resources. The clinical expert commented that both scenarios were broadly plausible but noted that people did not have annual GP check-ups in current clinical practice for GnRH antagonists. The committee acknowledged this and considered that it was not appropriate to model one year follow up GP assessments for GnRH antagonists but concluded that for the other healthcare resources both the EAG and company positions were plausible and appropriate for decision making.

Components of BSC

3.20 The company included NSAIDs and iron supplements as the main cost components of BSC. In the EAG base case the costs of vitamin D and calcium supplements were added to the cost of BSC after consultation with their clinical expert. The clinical expert considered that while there was emerging literature on the use of vitamin D as part of BSC for symptoms of uterine fibroids, they did not consider it to be part of current clinical practice. The committee considered the evidence and noted that inclusion of vitamin D and calcium supplements as part of BSC had a small effect on cost-effectiveness estimates. It concluded that both the company and EAG definitions of BSC were appropriate for decision making.

Cost effectiveness estimates

Acceptable ICER

3.21 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per quality adjusted life year (QALY) gained, decisions about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER, with the committee being more cautious about recommending a technology if it is less certain about the ICERs presented. The committee considered that there was unresolved

uncertainty in the clinical effectiveness evidence and cost effectiveness estimates (see sections 3.9 and 3.176). It concluded that the maximum acceptable ICER would be £20,000 per QALY gained.

Cost-effectiveness estimates

3.22 The committee recalled its preferred modelling assumptions on:

- using the UFS-QoL as a source for utilities in the model (see section 3.18)
- modelling of healthcare resource use (see section 3.19)
- components of BSC (see section 3.20)

The committee concluded that for the short-term usage population, the exclusion of GnRH agonists was not appropriate for decision making (see section 3.4). So, the committee were unable to make a positive recommendation in this population.

The EAG agreed with the company's updated model and assumptions and did not present an alternative base case. The company's deterministic ICER for linzagolix compared with relugolix CT in the longer-term with hormonal ABT population was £5,524 per QALY gained. The committee noted this ICER did not account for the considerable uncertainty around the results of the indirect treatment comparison. But it concluded that the true ICER is likely to be below £20,000 per QALY gained.

The company's deterministic ICER in the longer-term without hormonal ABT population was between £14,478 per QALY gained (EAG base case with their preferred assumption for healthcare resource) and £15,705 per QALY gained (EAG scenario including vitamin D and calcium supplements in BSC). Considering its view on the level of acceptable ICERs (see section 3.21), the committee concluded that linzagolix would

provide a cost-effective option for routine use in both the longer-term with hormonal ABT and longer-term without hormonal ABT populations.

Other factors

Equality

3.23 The committee considered that some people with uterine fibroids may be trans. Gender reassignment is a protected characteristic under the Equality Act 2010. The committee took this into account in its decision making. The committee recalled that Black women are more likely to have multiple fibroids that are large, so are more likely to need hospitalisation or surgical intervention. The committee also recalled the limitations of the EQ-5D when assessing quality of life for this condition, particularly concerning cyclical conditions (see section 3.18). It noted that one clinical expert stated that there are particular disadvantages associated with cyclical conditions, such as HMB and uterine fibroids, which predominately affect women. The committee recalled its preference for the UFS-QoL disease specific measure because it better captured quality of life in people with moderate to severe symptoms of uterine fibroids. The committee took into consideration the various equality issues raised. It considered that this recommendation provided a new treatment option for people with uterine fibroids, including those who cannot or would prefer not to have hormonal ABT.

Innovation

3.24 The committee considered whether linzagolix was innovative. It identified the flexibility of using linzagolix over existing treatments to be a potential additional benefit. Linzagolix has 2 licenced doses, and each can be used with or without hormonal ABT which offers clinicians and people greater flexibility and more individualised care in the treatment for moderate to severe symptoms of uterine fibroids. At present there are no longer term treatment options beyond BSC for people with moderate to severe symptoms of uterine fibroids who cannot have or do not want hormonal

ABT. Linzagolix provides an option to have a GnRH antagonist without hormonal ABT which meets a current unmet need.

Conclusion

Recommendation

3.25 The committee concluded that the most plausible ICERs were within the range it considered a cost-effective use of resources for the longer-term with hormonal ABT and without hormonal ABT populations. So, linzagolix with hormonal ABT at a dose of 200 mg could be recommended for the longer-term population. Linzagolix without hormonal ABT at a dose of 200 mg for 6 months followed by 100 mg afterwards could also be recommended as a treatment option for people who cannot or do not want hormonal ABT. The committee recalled that the cost-utility analysis of linzagolix for short-term usage without hormonal ABT had not included a comparison with GnRH agonists, so the committee was unable to establish whether linzagolix is a clinically and cost-effective option for people who need short-term treatment without hormonal ABT. It concluded that linzagolix was recommended only for longer-term use.

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 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 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 2 months 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 moderate to severe symptoms of uterine fibroids and is contraindicated to or prefers not to have hormonal add-back therapy the doctor responsible for their care thinks that linzagolix 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

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 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

Stephen O’Brien

Chair, technology appraisal committee C

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.

Samuel Slayen & Luke Cowie

Technical leads

Eleanor Donegan

Technical adviser

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Project manager

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