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SMC2631

linzagolix film-coated tablets (Yselty®)

Theramex Ireland Ltd

05 April 2024 *(Issued 04 October 2024)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

linzagolix (Yselty®) is accepted for restricted use within NHSScotland.

Indication Under Review: the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

SMC restriction: for use in patients when conventional first-line treatments (such as tranexamic acid, hormonal contraceptives and intrauterine devices) have failed or are considered unsuitable.

Treatment with linzagolix, with and without hormonal add-back therapy (ABT), resulted in statistically significant and clinically meaningful reductions in menstrual blood loss, compared with placebo.

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Linzagolix is an orally administered non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist. Inhibition of GnRH receptors in the anterior pituitary gland reduces the release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from this gland, ultimately leading to a suppression in estradiol (an oestrogen hormone) and progesterone production.[1-3]

The recommended dose of linzagolix is either 100 mg or, if needed, 200 mg once daily orally, with or without hormonal add-back therapy (ABT) which consists of norethisterone acetate 0.5 mg once daily and estradiol 1 mg once daily. Due to the risk of bone mineral density (BMD) decrease with prolonged use, linzagolix 200 mg daily should not be prescribed for >6 months without concomitant ABT. Further details are included in the summary of product characteristics (SPC).[1, 2]

1.2. Disease background

Uterine fibroids are benign smooth muscle tumours in the uterus that are hormone-sensitive, requiring oestrogen for growth, although this is also influenced by other hormones such as progesterone and local growth factors.[1, 3] Major risk factors for the development of uterine fibroids include race (where black women have a 2 to 3 fold-increased risk compared to white women)[1, 4] and age, with their prevalence increasing up to the menopause when the fibroids typically shrink and become inactive.[1, 3] It is estimated that uterine fibroids affect around 40% of women aged between 35 and 55 years old, and by 50 years of age approximately 70% of white women and 80% of black women will have had at least one fibroid.[1, 3, 5]

Around 30% to 40% of women are asymptomatic, with 15% to 30% having severe symptoms that require treatment. Symptoms typically experienced include heavy menstrual bleeding which may lead to iron deficiency anaemia; they may also experience pelvic pain, irregular bleeding or gastrointestinal upset (constipation, bloating or diarrhoea). Uterine fibroids are associated with infertility or problems during pregnancy.[1, 3]

1.3. Company proposed position

The submitting company has requested that linzagolix is restricted for use as a second-line therapy when conventional first-line treatments (such as tranexamic acid, hormonal contraceptives and intrauterine devices) have failed or are considered unsuitable.

1.4. Treatment pathway and relevant comparators

For patients with uterine fibroids and heavy menstrual bleeding, initial treatment options may include tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs), levonorgestrel-releasing intra-uterine system and hormonal contraceptives.[1, 6]

After these treatments, ulipristal acetate (a progesterone antagonist) is an option. However, following reported cases of serious liver injury and failure, ulipristal acetate is now restricted for use as intermittent treatment of pre-menopausal patients with moderate to severe symptoms of uterine fibroids when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed.[7]

Other subsequent treatment options include uterine artery embolisation or surgeries, such as hysterectomy or myomectomy. Pre-treatment with a GnRH agonist before hysterectomy and myomectomy can be considered if uterine fibroids are causing an enlarged or distorted uterus.[1, 6] However, their use is limited to 3 to 6 months as they reduce oestrogen to castration levels, which can cause menopausal symptoms and a loss of BMD. In practice, ABT can be combined with GnRH agonists to reduce menopausal symptoms and effects on BMD thereby allowing longer duration of treatment.[1]

Relugolix combination therapy (CT), consisting of the oral GnRH receptor antagonist, relugolix, and the oral ABT (norethisterone acetate 0.5 mg and estradiol 1 mg) is accepted for restricted use within NHSScotland for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age in patients who have failed or are unsuitable for conventional therapies (first line treatments), such as tranexamic acid, hormonal contraceptives and intrauterine delivery systems (SMC2442). This is in line with the company's proposed positioning for linzagolix.

The submitting company has considered relevant comparators according to three patient populations used in its cost-comparison and cost-effectiveness analyses. These include relugolix CT and the GnRH agonists (leuprorelin, goserelin, and triptorelin) for patients who will use linzagolix for ≤6 months (short-term; population 1); relugolix CT for patients who will use linzagolix for ≥6 months with ABT (longer-term; population 2); and best supportive care (BSC, defined as NSAIDs and iron supplements) for patients who will use linzagolix for ≥6 months without ABT (longer-term; population 3). These comparators seem relevant to practice.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the use of linzagolix for this indication comes from the PRIMROSE 1 and PRIMROSE 2 studies; these were similar in design. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	PRIMROSE 1 and PRIMROSE 2 studies.[1, 3]
Study Design	Multicentre, randomised, double-blind, parallel group, phase III studies.
Eligible Patients	• Pre-menopausal women aged ≥18 years with uterine fibroids and heavy menstrual bleeding (defined as ≥80 mL of menstrual blood loss per cycle for at least two cycles, as assessed by the AH method). • Experienced abnormal heavy menstrual bleeding (heavy or lasting >5 days) in most menstrual periods over the last 6 months. • Menstrual cycles lasted ≥21 days and ≤40 days prior to starting screening. • At least one fibroid of ≥2 cm diameter (or multiple small fibroids with a calculated uterus volume of >200 cm^3) and no fibroid with a diameter >12 cm. • No women with subserosal, pedunculated fibroids (FIGO classification type 7).
Treatments & randomisation	Patients were randomised equally to receive one of the following oral treatments for up to 52 weeks (but refer to specific footnotes): • 100 mg linzagolix once daily[a] • 100 mg linzagolix once daily plus hormonal ABT[b] once daily

	• 200 mg linzagolix once daily[a,c] • 200 mg linzagolix once daily plus hormonal ABT[b] once daily • Placebo once daily[a,d] Randomisation was stratified by race (Black/non-Black).
Primary outcome	Reduced menstrual blood loss at 24 weeks of treatment (last 28 days prior to the week 24 visit), defined as menstrual blood loss ≤80 mL and ≥50% reduction from baseline.
Secondary outcomes	• Time to reduced menstrual blood loss up to week 24.[e] • Amenorrhoea up to week 24.[f] • Time to amenorrhoea up to week 24. • Number of days of uterine bleeding for the last 28-day interval prior to week 24. • Haemoglobin levels at week 24 in a pre-specified group of anaemic patients.[g]
Statistical analysis	In both studies, menstrual blood loss was assessed using the AH method; the primary efficacy analysis was conducted after 24 weeks and used AH method data only. The primary efficacy analyses were performed in the FAS populations, which included all randomised patients who received at least one dose of double-blind study medicine. A hierarchical testing strategy was applied in each study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. The order of the hierarchical testing was the primary outcome, followed by the secondary outcomes within each linzagolix treatment group in the order above.

Abbreviations: ABT = add-back therapy; AH = alkaline haematin; BMD = bone mineral density; FAS = full analysis set; FIGO = International Federation of Gynaecology and Obstetrics

[a]these patients were also given a placebo form of hormonal add-back therapy in order to maintain study blinding.

[b]hormonal ABT consisted of 1 mg estradiol and 0·5 mg norethisterone acetate.

[c]after 24 weeks, all patients allocated to this group received ABT instead of the placebo form of ABT.

[d]after 24 weeks, 50% (PRIMROSE 1) and 100% (PRIMROSE 2) of patients allocated to this group were switched to receive 200 mg linzagolix plus hormonal ABT once daily; in PRIMROSE-1 the other 50% of patients remained on placebo (this process was randomised).

[e] defined as the number of days from day 1 of treatment to the first day in which the patient reached the definition of reduced menstrual blood loss (that is ≤ 80 mL and ≥ 50% reduction from baseline) and this was maintained up to 24 weeks.

[f] amenorrhoea (absence of menstrual bleeding) was determined using the alkaline haematin (AH) method, and defined as having no sanitary material returned (or the menstrual blood volume was less than the lower limit of quantification) over at least a 35-day interval.

[g] Anaemia was defined as a haemoglobin <12 g/dL.

In both PRIMROSE 1 and PRIMROSE 2, after 24 weeks (at the primary efficacy analysis) a higher proportion of women had a reduction in heavy menstrual bleeding (primary outcome) in all linzagolix treatment groups (with or without ABT) compared with placebo. Additionally, there was a difference in treatment effect for all hierarchically tested secondary outcomes (see table 2.1) that favoured all linzagolix treatment groups compared with placebo. An effect on reduced menstrual blood loss and amenorrhoea were seen as early as week 4; as shown by the Kaplan-Meier estimates. These differences were all statistically significant, except for the improvement in haemoglobin levels at week 24 for the linzagolix 100 mg group (PRIMROSE 1 only).[1, 3]

Efficacy data up to week 24 from the pooled full analysis set (FAS) of both studies is presented in Table 2.2, since this was the primary source for the clinical data in the cost effectiveness analyses. No adjustment was made for multiplicity within the pooled analysis, therefore, these results are considered descriptive only. These were largely consistent with those observed in the individual studies, PRIMROSE 1 and PRIMROSE 2.

Table 2.2: Primary and selected secondary outcomes at week 24 in the pooled FAS (PRIMROSE 1 and PRIMROSE 2).[1, 3]

	Placebo (n=205)	Linzagolix 100 mg (n=191)	Linzagolix 100 mg + ABT (n=208)	Linzagolix 200 mg (n=208)	Linzagolix 200 mg + ABT (n=200)
Primary outcome: proportion of patients with reduced HMB at week 24					
Responders, %	32%	57%	72%	75%	85%
Secondary outcome: time to reduced menstrual blood loss up to week 24[a]					
Hazard ratio (95% CI) versus placebo	-	2.10 (1.54 to 2.85)	4.33 (3.22 to 5.81)	4.29 (3.20 to 5.74)	5.73 (4.28 to 7.67)
KM probability estimate at week 4 (95% CI)	0.08 (0.05 to 0.12)	0.23 (0.18 to 0.30)	0.59 (0.52 to 0.65)	0.58 (0.52 to 0.65)	0.68 (0.62 to 0.75)
Secondary outcome: proportion of patients with amenorrhoea at week 24[b]					
Responders, %	17%	36%	52%	65%	69%
Odds Ratio (95% CI) versus placebo	-	2.84 (1.77 to 4.56)	5.40 (3.43 to 8.49)	8.99 (5.68 to 14.24)	10.25 (6.42 to 16.35)
Secondary outcome: time to amenorrhoea up to week 24					
KM probability estimate at week 4 (95% CI)	0.04 (0.02 to 0.08)	0.15 (0.10 to 0.21)	0.31 (0.25 to 0.38)	0.49 (0.43 to 0.56)	0.48 (0.41 to 0.55)
Secondary outcome: number of days of uterine bleeding for the last 28-day interval prior to week 24					
Mean number of days of bleeding	3.8	2.3	1.9	1.1	1.5
Secondary outcome: change in haemoglobin concentration at week 24 in a subset of patients with anaemia at baseline					
Patients with anaemia[c] at baseline in the FAS, n (%)	127 (62%)	129 (68%)	145 (70%)	133 (64%)	128 (64%)
Mean change in haemoglobin at week 24 from baseline (g/dL)	0.34	1.36	1.88	2.16	2.13

ABT = add-back therapy; CI = confidence interval; FAS = full analysis set; HMB = heavy menstrual bleeding; KM = Kaplan-Meier.

[a] defined as the number of days from day 1 of treatment to the first day in which the patient reached the definition of reduced menstrual blood loss (that is ≤ 80 mL and ≥ 50% reduction from baseline) and this was maintained up to 24 weeks.
[b] amenorrhoea (absence of menstrual bleeding) was determined using the alkaline haematin (AH) method, and defined as having no sanitary material returned (or the menstrual blood volume was less than the lower limit of quantification) over at least a 35-day interval.
[c] defined as a haemoglobin <12 g/dL.

Pooling of the study data was not carried out beyond week 24 as only PRIMROSE 1 had a placebo-control group beyond week 24. However, results at week 52 are available in both individual studies for patients who continued treatment after 24 weeks. The proportion of patients with reduced menstrual blood loss was maintained or increased at week 52 compared to week 24.[1] At week 52 in the linzagolix 100 mg, 100 mg plus ABT, and 200 mg with ABT groups, the percentage of responders was 57%, 80% and 88% in PRIMROSE 1, and 53%, 91% and 92% in PRIMROSE 2, respectively.[2, 3]

2.2. Evidence to support the positioning proposed by the submitting company

The submitting company did not provide specific clinical evidence to support the proposed positioning of linzagolix for use when conventional first-line treatments have failed or are

considered unsuitable. However, they noted that as reasons for suitability relate to inability to comply with treatment, a contraindication or desire to remain fertile rather than to demographic or disease characteristics, there is no reason to believe that efficacy in this group of patients would differ from that of the PRIMROSE study populations.

2.3. Health-related quality of life (HRQoL) outcomes

Health-related quality of life (HRQoL) was assessed in both studies as additional secondary outcomes using the Uterine Fibroid Symptoms Quality of Life and HRQoL (UFS-QoL-HRQoL) questionnaire total score and the UFS-QoL symptom severity questionnaire score. In both studies, higher total scores and lower symptom severity scores, both indicating improvement, were observed at 24 weeks in all linzagolix groups (with and without ABT) compared with placebo. These improvements were observed in all domains (concern, activities, energy and mood, control, self-consciousness, and sexual function) and maintained up to week 52 in the PRIMROSE 2 study.[1, 3]

EQ-5D-5L data was also collected at weeks 12, 24, 36, 52, and 64 in both studies. Results reported at week 24 have indicated small increases in EQ-5D-5L index values and visual analogue scale scores in all treatment groups including placebo and no noticeable differences between linzagolix and placebo.[1] These data were not used in the economics base case.

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing linzagolix with relugolix CT, the company conducted a network meta-analysis (NMA) to assess the effectiveness of linzagolix (100 mg or 200 mg) with and without ABT and relugolix CT using placebo as a common comparator. The results of the NMA were not used to inform the economic model for this submission but were used to support the company's assumption that linzagolix and relugolix CT are considered to have comparable clinical efficacy. A matching adjusted indirect comparison (MAIC) was also considered as a scenario analysis to explore whether differences in baseline characteristics may have impacted comparative results from the NMA. Overall, the NMA results did not indicate any consistent or substantial differences in treatment efficacy for linzagolix when compared with relugolix CT for outcomes including mean blood loss, change in fibroid volume, and changes in haemoglobin.

3. Summary of Safety Evidence

In the PRIMROSE 1 and PRIMROSE 2 studies, the safety profile for linzagolix was consistent with that expected for a GnRH antagonist. Overall, linzagolix appeared to be well-tolerated with the most common adverse events (AEs) such as hot flushes, headaches, and night sweats, expected of a medicine that causes oestrogen suppression. The incidence of these AEs increased with higher doses of linzagolix and were attenuated by the addition of ABT.[1]

A treatment-emergent AE was reported in 51% to 63% of patients in the linzagolix groups compared with 49% in the placebo groups. The majority of treatment-emergent AEs were mild to moderate in severity, and only 0.5% to 2.4% versus 1.9% respectively were considered serious. In the pooled safety populations in both studies, the incidence of treatment-emergent AEs that resulted in treatment discontinuation at week 24 were relatively low and comparable between the placebo group (8.1%) and all the linzagolix treatment groups (between 7.0% and 11%); this

incidence was highest in the 200 mg linzagolix alone group. At week 52, there were fewer treatment-emergent AEs reported compared to week 24, despite the fact most patients remaining in the study were on active treatment. [1]

BMD loss was an AE of special interest and assessed as an exploratory outcome using dual energy X-ray absorptiometry (DXA) scans in both studies. Dose- and time-dependent changes in BMD were observed in all linzagolix groups, and the addition of ABT attenuated some BMD loss. At week 24, in the pooled analysis of the safety populations in both studies, the greatest reduction in BMD was in the linzagolix 200mg group (-3.7%), followed by the linzagolix 100mg group (-1.99%) and with the smallest reduction (of similar magnitude) in the linzagolix 200mg + ABT, and linzagolix 100mg + ABT groups (-1.13% and -0.96%, respectively). Available data suggest a trend of reversibility or partial reversibility by 6 months after stopping trial therapy; full or partial recovery of lumbar spine BMD was achieved by 53%, 52% and 64% for linzagolix 100 mg, 100 mg with ABT and 200 mg with ABT, respectively in PRIMROSE 1 and 59%, 80% and 67% for linzagolix 100 mg, 100 mg with ABT and 200 mg with ABT in PRIMROSE 2.[1, 2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- PRIMROSE 1 and PRIMROSE 2 were well-conducted, randomised, double-blind, phase III studies with stratification, and most baseline characteristics were balanced between all the treatment groups; this makes it likely that there is a low risk of bias.
- In PRIMROSE 1 and PRIMROSE 2, compared with placebo, treatment with linzagolix 100 mg or 200 mg daily (with and without ABT) resulted in statistically significant and clinically meaningful reductions in menstrual blood loss, and almost all key secondary outcomes at week 24. This treatment effect was maintained or increased at week 52.[1] The largest treatment effects were seen in patients in the 200 mg plus ABT group (full suppression) compared to the 100 mg groups (considered partial suppression).[1, 2]

4.2. Key uncertainties

- Patients in the PRIMROSE studies were not required to have failed or be unsuitable for conventional first-line therapies and the company did not provide any specific evidence to support the proposed positioning as a second-line therapy. The company considered that the efficacy of linzagolix in the second-line setting would be similar to that in the PRIMROSE study populations.
- There is a lack of direct comparative evidence with other treatment options that may be used in these patients. The company performed an NMA versus relugolix CT and results were used to support the company's assumption of comparable clinical efficacy between linzagolix and relugolix CT. There were a number of limitations including heterogeneity across baseline characteristics of the study populations. The NMA results generally included the null effect indicating no evidence of a treatment difference, but the credible intervals were wide indicating uncertainty. In addition, there was inconsistency in the direction of the treatment

effect with point estimates for some outcomes favouring linzagolix, some relugolix CT and some neither. Therefore, there may be uncertainties in the assumption of clinical equivalence.

- The SPC does not give advice of overall treatment duration but safety data are only available for up to 52 weeks of linzagolix treatment and the treatment effects and BMD loss after this time period are unknown.[2] The SPC includes recommendations regarding DXA scans and further information regarding risk factors for osteoporosis and bone loss.[2]
- The results of the pooled analysis of PRIMROSE 1 and 2 were considered exploratory/descriptive only. Despite being very similar in design, there were notable differences between the PRIMROSE 1 (conducted in the US alone) and PRIMROSE 2 studies (conducted in US and 8 European countries) that could affect the generalisability of the study findings. Compared with PRIMROSE 2, PRIMROSE 1 had much higher proportions of: black patients (63% versus 5.0%) and dropout rates at week 24 (32% versus 15%). Whilst the results of PRIMROSE 2 showed a larger treatment effect than PRIMROSE 1, this population may be more generalisable to Scottish patients; therefore, the pooling of data may yield more conservative results.
- It was noted that there was a 32% response rate (in the pooled FAS) in the placebo group for the primary outcome. The primary outcome was measured using returned used sanitary products, and if no products were returned this was considered as no bleeding for that day. Patients unable to return sanitary products on days of menstrual blood loss may lead to an overestimation in the reduction in MBL. However, regression to the mean could also be another reason for the observed placebo effect.

4.3. Clinical expert input

Clinical experts consulted by SMC considered linzagolix a therapeutic advancement and noted that it offers another oral treatment option for these patients. Some experts also highlighted it could reduce the number of hysterectomy and fibroid embolisation procedures. The flexibility in dosing (100 mg or 200 mg dose) and the option to administer with or without concomitant ABT could be advantageous for certain groups of patients.

4.4. Service implications

No significant service implications are anticipated.

5. Summary of Patient and Carer Involvement

No patient group submission was received.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	The economic approach used differed depending on the population under consideration (details of the populations are provided below). Cost-minimisation analyses were presented for population 1 and 2, and a cost-utility analysis for population 3.
Time horizon	For population 1, a time horizon of 6 months was used given the short-term treatment. For long-term uses (populations 2 and 3), a time horizon of 10 years was used to capture the differences between the treatments based on the average age of the cohort at baseline (42 years) and the average age of menopause in the UK (52 years).
Population	The analysis covered 3 distinct patient populations: • Population 1: patients having short-term treatment of 6 months or less. • Population 2: patients having longer-term treatment, with ABT. • Population 3: patients having longer-term treatment, without ABT.
Comparators	For populations 1 and 2, the main comparison was with relugolix CT. For population 1 a secondary comparison with GnRH agonists leuporelin, goserelin and triptorelin was provided. For population 3 the comparator was BSC which included NSAIDs and iron supplements.
Model description	For populations 1 and 2, a simple cost-minimisation analysis was provided comparing the costs of the intervention and comparators, including medicine acquisition, administration, concomitant medications, resource use and surgery costs. For population 3, a cohort-level Markov model was submitted with 4 health states related to symptom control and surgery: controlled, uncontrolled, surgery and post-surgery, plus additional health states of menopause and death. All patients entered the model in the 'uncontrolled' health state with moderate to severe UF symptoms and receive treatment with either linzagolix or BSC. Patients can then remain 'uncontrolled' or 'controlled' after treatment. Symptom control was defined in the model according to the primary endpoint of the PRIMROSE 1 and 2 studies, with uncontrolled symptoms were defined by HMB > 80mL MBL per cycle and controlled disease defined as MBL <80ML AND >50% reduction from baseline. Surgery included uterine artery embolisation, magnetic- resonance-guided focused ultrasound, myomectomy or hysterectomy and was assumed to last for 1 model cycle after which patients moved to the post-surgery health state.
Clinical data	To support the assumption of comparable efficacy required for the cost-minimisation analyses, the company highlighted the lack of evidence to show a difference between linzagolix and relugolix CT from the NMA, in addition to clinical opinion and previous SMC and NICE technology appraisals (SMC2442 and TA832). For the cost-utility analysis, the pooled PRIMROSE 1 and 2 studies were the key data sources and it was assumed the placebo arm was representative of BSC. The model used baseline characteristics, 24-week response data and adverse event rate data from the pooled PRIMROSE studies. Surgery rates were not available from the PRIMROSE studies so were taken from PEARL II, which compared ulipristal acetate with leuporelin acetate for the pre-operative treatment of fibroids. This study reported a surgery rate of 45.1%.[8]

Extrapolation	Recurrence rates in the cost-utility analysis estimating the probability of losing response and moving from the 'controlled' to the 'uncontrolled' health state were informed by a company market research study of UK gynaecologists. To extrapolate the 24-week response data beyond the end of the studies the company used an exponential model to estimate the 28-day cycle probability of moving from the 'uncontrolled' to 'controlled' health state.
Quality of life	UFS-QoL data were collected in the PRIMROSE studies and mapped to EQ-5D to derive utility values for use in the model. Surgery and post-surgery utility values were estimated by weighing values from several published sources.
Costs and resource use	Costs included medicine acquisition, administration and concomitant medicine costs. All patients were assumed to require medication for pain and blood loss. Surgery costs were treatment-independent and surgery type was included according to the proportions used in NICE TA832, with most patients (51.8%) assumed to require abdominal hysterectomy.
PAS	There is no patient access scheme included with this advice.

6.2. Results

The company provided base case results across the three separate population. The results for population 1 and 2, where a cost minimisation analysis was used, are commercial in confidence, meaning SMC is unable to publish them.

For population 3, the cost-utility analysis estimated that linzagolix was associated with improved health, but also higher costs for the NHS. The base case incremental cost effectiveness ratio (ICER) was estimated as being £15,392.

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

Sensitivity and scenario analyses were used to explore areas of uncertainty in the economic analysis. Again, for populations 1 and 2 results cannot be presented, as they are marked as commercial in confidence by the submitting company. However, the scenarios considered most relevant to decision making are detailed in Tables 6.3a and 6.3b.

A selection of the most relevant scenarios exploring uncertainty in the economic results for population 3 are shown in Table 6.3c, alongside the ICERs.

Table 6.3a Sensitivity analysis: Cost- Minimisation Analysis, Population 1 – short-term treatment

Base case	Scenario
GnRH agonist formulation, 1 monthly	3 monthly
Surgery probability, 45.1%	100%
Distribution of surgery types, treatment independent (TA832)	10% more in linzagolix/GnRH arms receive laparoscopic surgery instead of abdominal surgery

Abbreviations: GnRH = gonadotropin-releasing hormone, TA = NICE technical appraisal

Table 6.3b Sensitivity analysis: Cost- Minimisation Analysis, Population 2 – long-term treatment with hormone-based therapy

Base case	Scenario
Time horizon 10 years	5 years
Surgery probability 45.1%	25%
Linzagolix dose 200mg + ABT and treatment independent surgery type distributions	200mg for 6 months, followed by linzagolix 200mg + ABT and 10% more in linzagolix arm receive laparoscopic surgery instead of abdominal surgery

Abbreviations: ABT = add-back therapy, mg = Milligram

Table 6.3c Sensitivity analysis: Cost- Utility Analysis, Population 3 – long-term treatment without hormone-based therapy

	Base case	Scenario	ICER (£/QALY)
	Base case		£15,392
1	Linzagolix dosing 200mg for 6 months followed by 100mg	100mg	£17,365
2	Recurrence rate by treatment	Assumed equal to BSC	£20,707
3	Surgery distribution from TA832	10% more in linzagolix arm receive laparoscopic surgery instead of abdominal surgery	£12,519
4	BSC response % (24-week)	Upper bound	£19,035
5	Treatment withdrawal rates from trial	Modified trial rates (AEs as the reason for discontinuation)	£25,828
6	Utility data from UFS-QoL in PRIMROSE studies mapped to EQ-5D	EQ-5D data from PRIMROSE studies	£30,803
7	Combined analysis: scenarios 2, 4 + 5 combined		£46,968
8	Combined analysis: scenarios 6 + 7 combined		£95,510

Abbreviations: ICER = Incremental cost-effectiveness ratio, QALY = Quality adjusted life year, mg = Milligram, BSC = Best supportive care, TA = NICE technical appraisal, AE = Adverse event, UFS-QoL = Uterine Fibroid Symptoms Quality of Life questionnaire, EQ-5D = EuroQol 5-Dimmensions questionnaire

6.4. Key strengths

- The model was relatively simple and methods clearly explained.
- Quality of life data (EQ-5D and UFS-QoL) were collected directly from patients within the studies for use in the model.

6.5. Key uncertainties

- The clinical evidence presented to show comparable efficacy between linzagolix and the comparators is uncertain, meaning it was also uncertain whether the cost-minimisation analysis approach taken in populations 1 and 2 was appropriate. The limitations of the NMA described above suggest there could be differences in efficacy between the treatments that have not been captured in the economic analysis.
- Within the PRIMROSE studies, quality of life information was collected using the generic EQ-5D and the condition specific UFS-QoL instruments. Within the base case, UFS-QoL data were

mapped to EQ-5D using an unpublished algorithm to derive utility values for use in the model. The company justified this approach on the basis that the EQ-5D questionnaire is not sensitive enough to capture quality of life differences in patients with uterine fibroids due to the cyclical nature of the condition. However, the mapping approach is also associated with uncertainty. Sensitivity analysis showed using the EQ-5D data directly, resulted in less favourable economic results (see Scenario 6 in Table 6.3c).

- There were some limitations with the clinical data underpinning the model, including some concerns about the generalisability of the data to the proposed second-line positioning and specifically to the three patient populations used in the economic analysis. If the treatment benefit of linzagolix within the real-world treatment population differed from that estimated in the studies, this would impact upon the economic results.

7. Conclusion

After considering all the available evidence, the Committee accepted linzagolix for restricted use in NHSScotland.

8. Guidelines and Protocols

The National Institute of Health and Care Excellence (NICE) guideline 88 (NG88), heavy menstrual bleeding: assessment and management was published in March 2018 and updated in May 2021.[6]

9. Additional Information

9.1. Product availability date

23 September 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Linzagolix 100 mg or 200 mg film-coated tablets	**One tablet once daily, with or without concomitant hormonal add-back therapy***	Without add-back therapy: £1,040 With add-back therapy: £1,098

**add-back therapy consists of 1 mg oestradiol and 0.5 mg norethisterone acetate once daily.*

Costs from the company and the Dictionary of Medicines and Devices (DM+D) database on 15 July 2024.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The company estimated there would be 6,718 patients eligible for treatment with linzagolix each year.

SMC is unable to publish the impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted

budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

References

1. European Medicines Agency (EMA). European Public Assessment Report. linzagolix (Yselty®). 02/05/2023, EMEA/H/C/005442/0000. www.ema.europa.eu 2023.
2. Theramex Ireland Ltd. Linzagolix 100 mg and 200 mg film-coated tablets (Yselty®) Summary of product characteristics. Medicines and Healthcare products Regulatory Agency (MHRA). Available from: https://products.mhra.gov.uk/substance/?substance=LINZAGOLIX%20CHOLINE [Accessed: 22 Jan 2024].
3. Donnez J, Taylor HS, Stewart EA, Bradley L, Marsh E, Archer D, *et al.* Linzagolix with and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids: two randomised, placebo-controlled, phase 3 trials. The Lancet. 2022;400(10356):896-907. 10.1016/S0140-6736(22)01475-1
4. Stewart E, Cookson C, Gandolfo R, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG: An International Journal of Obstetrics & Gynaecology. 2017;124(10):1501–1512.
5. Al-Hendy A, Myers ER, Stewart E. Uterine Fibroids: Burden and Unmet Medical Need. Semin Reprod Med. 2017 Nov;35(6):473–480.
6. National Institute for Health and Care Excellence (NICE). NICE guideline 88 [NG88] - Heavy menstrual bleeding: assessment and management. Published: March 2018; Updated: 24 May 2021. Accessed: 05 February 2024. Available at: https://www.nice.org.uk/guidance/ng88.
7. Gedeon Richter (UK) Ltd. Ulipristal acetate 5 mg Tablets (Esmya®) Summary of product characteristics. Electronics Medicines Compendium www.medicines.org.uk. Last updated: 17 Feb 2021.
8. Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuk B, Baró F, *et al.* Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med. 2012;366(5):421-32. 10.1056/NEJMoa1103180

This assessment is based on data submitted by the applicant company up to and including 25 September 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates

separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.