NCPE Assessment Summary

Linzagolix choline/Yselty®

HTA ID: 23068

August 2026

Applicant: Theramex

Linzagolix choline for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of linzagolix (Yselty®) for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Following assessment of the Applicant's submission, the NCPE recommends that linzagolix (Yselty®) be considered for reimbursement, if cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Theramex) Health Technology Assessment of linzagolix (Yselty®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In December 2025, Theramex submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of linzagolix (Yselty®) for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. Theramex is seeking reimbursement of linzagolix on the High-Tech Drug Arrangement.

Uterine fibroids are very common benign growths that develop in the muscular wall of the uterus. Uterine fibroids are generally diagnosed in the late reproductive stage. Typically, uterine fibroids regress in individuals who are post-menopausal, likely due to the ovaries producing diminishing levels of oestrogen. The presentation of uterine fibroids can vary considerably, depending on location and size. While some uterine fibroids remain asymptomatic, some can cause debilitating symptoms including frequent pressure pain, subfertility and more commonly heavy or prolonged menstrual bleeding. Uterine fibroids may be treated by pharmacological therapies. Hormonal therapies (levonorgestrel intrauterine system, combined oral contraceptives, norethisterone and injectable long-acting progestogens) are commonly prescribed first-line. Non-hormonal options include non-steroidal anti-inflammatory drugs and tranexamic acid. Radiological or surgical interventions may also be considered. These interventions range from minimally invasive procedures such as uterine artery embolisation, transvaginal resection and ablation to more invasive procedures such as myomectomy or hysterectomy. Gonadotropin-releasing hormone (GnRH) agonists (e.g. goserelin, leuprorelin, triptorelin) can be prescribed in order to reduce fibroid or uterine volume prior to radiological or surgical intervention.

Linzagolix is a selective, non-peptide GnRH receptor antagonist that inhibits endogenous GnRH signalling by binding competitively to GnRH receptors in the pituitary gland, thereby modulating the hypothalamic-pituitary-gonadal axis. Administration of linzagolix results in dose-dependent suppression of luteinizing hormone and follicle-stimulating hormone, leading to decreased blood concentrations of oestradiol and progesterone. Linzagolix tablets are available in two strengths; 100mg and 200mg. The recommended dose for the treatment

of moderate to severe symptoms of uterine fibroids is 100mg or, if needed, 200mg once daily with concomitant hormonal add-back therapy (ABT). A dose of 100mg once daily is recommended for individuals in whom ABT is not recommended or who prefer to avoid hormonal therapy. A dose of 200mg once daily is recommended for short-term use (less than six months) in clinical situations when reduction of uterine and fibroid volume is desired. In relation to the short-term dosage regimen the product licence highlights that fibroid size may increase when the treatment is stopped. The product licence states that due to the risk of bone mineral density (BMD) decrease with prolonged use, the 200mg dose without concomitant ABT should not be prescribed for longer than six months.

Theramex is seeking reimbursement in two subpopulations; a surgical subpopulation and a long-term subpopulation. The surgical subpopulation represents patients who require a short-term course of treatment with medical therapy prior to surgical intervention to shrink uterine fibroids and manage other symptoms. The long-term subpopulation represents patients for whom first-line hormonal treatments have failed and are ineligible for or opt to avoid surgical interventions. For patients eligible and opting for surgery, GnRH agonists (goserelin, leuprorelin, triptorelin) are the most relevant comparators. For patients in the second-line setting who are ineligible for or who have opted against surgery, best supportive care (BSC) no active pharmacological treatment), is considered to be the most relevant comparator. The Applicant's proposed place in therapy is narrower than the licensed indication, as the Applicant anticipates linzagolix will only be used second-line in the long-term subpopulation

1. Comparative effectiveness of linzagolix

The clinical trial programme of linzagolix included two phase III trials, PRIMROSE 1 and PRIMROSE 2, which investigated the efficacy and safety of linzagolix compared with placebo for the treatment of moderate to severe symptoms of uterine fibroids. PRIMROSE 1 and PRIMROSE 2 were almost identical in design. PRIMROSE 1 was conducted exclusively in the US while PRIMROSE 2 enrolled participants in Europe (91%) and the US (9%). The trials enrolled women with uterine fibroids and heavy menstrual bleeding. Those with severe uterine fibroids which would require surgery within six months regardless of treatment provided were excluded. The primary efficacy endpoint (reduced menstrual blood loss

[MBL]) was measured as the proportion of women who achieved a MBL less than or equal to 80 mL alongside a 50% reduction in MBL from baseline at 24 weeks.

In both trials patients were randomised in a 1:1:1:1:1 ratio to receive once daily doses of either linzagolix 100mg, linzagolix 100mg + ABT, linzagolix 200mg, linzagolix 200mg + ABT or placebo. The full analysis set evaluated in the PRIMROSE 1 and PRIMROSE 2 trials comprised 511 and 501 participants, respectively. Across the two trials, the mean age of women was 42 years (range 20 to 58 years). Approximately 34.5% of women were Black, 63.5% were White and 2% were of another race. The most commonly reported symptoms in addition to heavy menstrual bleeding were abdominal pain (67.9%), abdominal pressure (52.5%), menstruation lasting longer than usual (50.4%), lower back pain (50.2%), increased urinary frequency (34.5%) and pain during intercourse (27.7%). Almost all women (99.7%) had at least one fibroid greater than or equal to 2cm in length and 97.5% had an International Federation of Gynaecology and Obstetrics (FIGO) classification from Type 1 to 6. Differences in some baseline characteristics were noted between the two PRIMROSE trials in terms of race, weight and body mass index. The number of prior medical interventions participants had received for uterine fibroids was not accurately captured due to high variability in how historical treatments were categorised and recorded across trial sites.

In both PRIMROSE 1 and PRIMROSE 2, the primary endpoint was met. In the pooled results reduced MBL at Week 24 was achieved in 84.5%, 74.5%, 71.6%, 56.5% of patients in the linzagolix 200mg + ABT, linzagolix 200mg, linzagolix 100mg + ABT and linzagolix 100mg arms respectively compared with 32.2% of patients in the placebo arm ($p < 0.001$ for all comparisons with placebo). Overall, the uterine and fibroid volume changes observed across the PRIMROSE 1 and 2 trials in the linzagolix 200mg groups were clinically relevant with reductions from baseline of 39% and 48% observed for uterine and fibroid volumes, respectively. Smaller reductions in uterine and fibroid volume were observed in the other arms. Health-related quality of life (HRQoL) was assessed using the uterine fibroid symptom and HRQoL questionnaire (UFS-QoL) and the EQ-5D. In the pooled analysis, there were decreases in the symptom severity scores (indicating improvement) and increases in the HRQoL total scores (indicating improvement) from baseline at Week 24 in the linzagolix groups compared with the placebo group (nominal $p < 0.001$ all comparisons).

The Review Group has concerns that women requiring surgery within six months were excluded from participation in the PRIMROSE 1 and 2 trials. The PRIMROSE trials also do not provide direct comparative evidence for linzagolix against GnRH agonists, which are the main comparators of relevance in the surgical subpopulation, for whom reimbursement is also being sought. Furthermore, the trial populations comprised women receiving first and subsequent line therapies for uterine fibroids. In the case of the long-term subpopulation, Theramex is seeking reimbursement of linzagolix in the second-line setting only for patients who are ineligible for or have opted against surgery.

Indirect treatment comparison:

At the time of HTA submission, head-to-head trials were only available to provide direct comparative evidence for linzagolix (with or without ABT) versus placebo, presented as a proxy for BSC by the Applicant. Indirect comparative methods, via network meta-analysis (NMA) were used to inform the comparison between linzagolix and leuprorelin, which was assumed to be equivalent to other GnRH agonists in this indication. In addition to the PRIMROSE I and II trials, the evidence network included the PEARL II trial comparing leuprorelin with ulipristal acetate, and the PEARL I trial comparing ulipristal acetate with placebo. Four outcomes were included in the Applicant's NMA: bleeding response, amenorrhea, total fibroid volume, and haemoglobin. In the base case analysis, 24-week outcomes from the PRIMROSE trials were combined with 13-week outcomes from PEARL I and II. An additional scenario comparing 12-week outcomes from PRIMROSE with 13-week outcomes from PEARL I and II was also provided by the Applicant.

Results from the NMA suggest that linzagolix is less effective than the GnRH agonist, leuprorelin, for the outcomes of bleeding control and amenorrhea. Leuprorelin was also associated with greater reductions in fibroid volume compared to linzagolix with ABT, but not when compared to linzagolix without ABT. However, major differences between the included studies, including differences in patient populations, baseline characteristics and outcome definitions, seriously threaten the validity of the NMA results and it is not possible to draw definite conclusions regarding comparative effectiveness of linzagolix and GnRH agonists. The Review Group also note that results from the NMA are inconsistent with

recently published direct evidence from a randomised controlled trial which was not included in the original HTA submission. This study, conducted in Japan, indicated comparable efficacy of linzagolix 200mg and leuprorelin. However, the generalisability of this study findings to the patient population in Ireland is unclear.

2. Safety of linzagolix

Linzagolix was studied in 1,605 participants in pivotal controlled trials for up to six months or more. These trials included participants with uterine fibroids or endometriosis. The most common adverse reactions reported were hot flushes and headaches, which were reported with higher frequency at higher doses and less frequently when ABT was taken concomitantly. Hot flushes were reported in 5.2%, 9.6%, 10.1% and 31.0% of women treated with linzagolix 100mg + ABT, linzagolix 200mg +ABT, linzagolix 100mg and 200mg, respectively. Similarly, headaches were reported more frequently at higher doses of linzagolix and decreased when linzagolix was given with ABT (1.4%, 2.4%, 4.0% and 6.2% for 100mg + ABT, 200mg + ABT, 100mg and 200mg, respectively).

The safety data available demonstrates that all doses of linzagolix have the potential to negatively impact BMD. In the PRIMROSE 1 and 2 trials, dose- and time-dependent changes in BMD were observed. Reduction in BMD was highest in the linzagolix 200mg group. Concomitant ABT attenuated BMD loss. In some individuals treated with linzagolix, who had normal BMD at start of treatment, BMD loss varying from greater than 3 to 8% was reported. The product licence notes that the level of treatment induced BMD loss in this population considered to be clinically meaningful is not well established, and will depend on the individual, but in general BMD losses of approximately 3% or more should be reviewed and monitored carefully. At 24 weeks following treatment cessation, most patients had full or partial recovery of lumbar spine BMD.

PRIMROSE 3 was a long-term follow-up study on BMD in participants who completed at least 20 weeks of treatment in the PRIMROSE 1 and PRIMROSE 2 trials and underwent a DEXA scan within 35 days of their last treatment. Of the 1,037 participants initially recruited in the two PRIMROSE trials, 130 participants were included in the safety analysis set of PRIMROSE 3. The mean duration of therapy with linzagolix was 50.95 weeks. The results of PRIMROSE 3 demonstrated the mean changes in lumbar spine BMD two years post-treatment were small

across the linzagolix treatment groups and closely mirrored the variations observed in the placebo group. In patients with risk factors for osteoporosis or bone loss, a DEXA scan is recommended prior to starting linzagolix treatment. A DEXA scan is recommended after one year of treatment for all patients and there is a need for continued monitoring if treatment continues thereafter.

3. Cost effectiveness of linzagolix

The Applicant considered two subpopulations; a surgical subpopulation (comparison against GnRH agonists) and a long-term subpopulation (comparison against BSC). The intervention for the surgical subpopulation was linzagolix 200mg once daily for up to six months and linzagolix 200mg once daily + ABT for those who remained on linzagolix for more than six months. The intervention for the long-term subpopulation was assumed to be linzagolix 200mg once daily + ABT. A scenario whereby the patients in the long-term subpopulation receive linzagolix 100mg once daily was also included in the cost-effectiveness model (CEM).

Methods

The Applicant's CEM uses a cohort-level state transition approach. The model has a lifetime horizon (60-years) and a 28-day cycle length. Patients enter the model in the uncontrolled health state with heavy menstrual bleeding (defined as > 80mL MBL per 28-days). In each model cycle patients can transition to the controlled disease state, defined as MBL ≤ 80 mL and ≥ 50% reduction from baseline, corresponding to the primary efficacy endpoint definition in the PRIMROSE 1 and 2 trials. Patients may remain in the controlled state, or they may lose response and re-enter the uncontrolled state. Transitions to surgery, menopause or death health states are possible from both the controlled and uncontrolled states. Surgery consists of one of uterine artery embolisation, ablation (endometrial, fibroid, radiofrequency), transvaginal resection, myomectomy or hysterectomy, and patients may undergo up to three surgeries in total. The Review Group notes that the model relies on bleeding control as a surrogate outcome to capture the impact of treatment on HRQoL and surgery rates. Other patient-relevant outcomes (e.g. pain, fibroid volume, fibroid location) are not explicitly accounted for in the model structure.

Transition probabilities from the uncontrolled to controlled health states for linzagolix and

BSC were estimated using data from the pooled PRIMROSE 1 and 2 trials. Results from the Applicant's NMA were applied to estimate transition probabilities for GnRH agonists. The Applicant derived transition probabilities from controlled to uncontrolled from clinicians' estimates of annual recurrence rates collected in a survey of UK-based gynaecologists.

In the surgical subpopulation, the same probability of surgery was applied to both health states (controlled and uncontrolled) and was assumed to remain constant over time. In the long-term subpopulation, the Applicant assumes that only patients in the uncontrolled health state can undergo surgery. The probability of transition to surgery in both subpopulations was informed by surgery rates in the PEARL II trial, which enrolled participants with symptomatic uterine fibroids who were planning to undergo surgery. Estimates of HRQoL (utility values) collected in the PRIMROSE 1 and 2 trials were applied to the controlled and uncontrolled health states, while HRQoL in the surgery and post-surgery states was estimated using utility values obtained from the published literature.

The Review Group noted a number of limitations in the Applicant's base case which were addressed via changes to develop the NCPE adjusted base case. These included:

- Using a different approach to estimate transition probabilities from the uncontrolled to controlled health states after Week 24
- Estimating bleeding recurrence rates from clinical trial data
- Assuming that patients not responding to linzagolix after week 52 will discontinue treatment
- Using alternative data sources and assumptions to estimate surgery rates
- Estimating the HRQoL impact of bleeding control using utility values derived from EQ-5D (rather than UFS-QoL) data collected in the PRIMROSE 1 and 2 trials
- Using alternative utility data sources to estimate pre-surgery HRQoL in the surgical subpopulation
- Removing the HRQoL decrement associated with subcutaneous administration of GnRH agonists

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the Applicant and NCPE adjusted base cases for both the surgical and long-term subpopulations are shown

in Tables 1 and 2, respectively. The cost-effectiveness results for triptorelin are presented for the surgical subpopulation, as based on clinical opinion this is the most commonly used GnRH agonist in this setting.

Table 1: Applicant base case incremental cost-effectiveness results [a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER[a] (€/QALY)
Surgical subpopulation					
Triptorelin (GnRH agonist)	16,231	15.992	-	-	-
Linzagolix	17,532	16.018	1,301	0.026	50,435
Long-term subpopulation					
Best supportive care	13,550	15.920	-	-	-
Linzagolix[c]	17,064	16.037	3,514	0.118	29,848

GnRH: gonadotropin-releasing hormone; **ICER:** incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year

[a] Corresponding probabilistic ICER using 1,000 iterations is €48,329/QALY in the surgical subpopulation and €31,379/QALY in the long-term subpopulation. Figures in the table are rounded, and so calculations may not be directly replicable

[b] As packs are flat-priced the linzagolix 100mg packs should not be used to achieve a dose of 200mg once daily as otherwise the cost per patient will double

[c] Results are based on linzagolix 200mg once daily + ABT. The ICER based on linzagolix 100mg once daily is €45,815/QALY

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Table 2: NCPE adjusted base case incremental cost-effectiveness results [a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER[a] (€/QALY)
Surgical subpopulation					
Triptorelin (GnRH agonist)	14,404	15.693	-	-	-
Linzagolix	16,265	15.719	1,861	0.026	72,847
Long-term subpopulation					
Best supportive care	9,503	15.966	-	-	-
Linzagolix[c]	15,378	16.079	5,875	0.113	52,191

GnRH: gonadotropin-releasing hormone; **ICER:** incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year

[a] Corresponding probabilistic ICER using 1,000 iterations is €71,993/QALY in the surgical subpopulation and €52,175/QALY in the long-term subpopulation. Figures in the table are rounded, and so calculations may not be directly replicable

[b] As packs are flat-priced the linzagolix 100mg packs should not be used to achieve a dose of 200mg once daily as otherwise the cost per patient will double

[c] Results are based on linzagolix 200mg once daily + ABT. The ICER based on linzagolix 100mg once daily is €56,242/QALY

The Review Group considers the comparative- and cost-effectiveness of linzagolix in the surgical subpopulation to be particularly uncertain, and notes that the Applicant is seeking a substantial price premium over GnRH agonists. The QALY gain in the surgical subpopulation arises primarily because linzagolix (unlike GnRH agonists) may be continued as a long-term treatment in patients who ultimately do not undergo surgery. The effect of linzagolix on rates and types of surgical procedures received, and the relative impact on HRQoL of

pharmacological treatment compared to surgery, cannot be reliably determined from the available evidence.

Sensitivity analysis

The probability of cost-effectiveness for linzagolix versus its comparators are presented in Table 3.

Table 3: Probability of cost effectiveness for linzagolix versus relevant comparators (GnRH agonists/BSC)

Probability of cost effectiveness				
	Surgical subpopulation (vs GnRH agonists)		Long-term subpopulation (vs BSC)	
Threshold (€/QALY)	Applicant base case	NCPE adjusted base case	Applicant base case	NCPE adjusted base case
20,000	10.8%	0.0%	0.0%	0.0%
45,000	67.8%	0.2%	30.4%	8.2%

BSC: best supportive care; **GnRH:** gonadotropin-releasing hormone; **QALY:** quality-adjusted life year

[a] Results based on probabilistic analysis using 1,000 iterations

Deterministic one-way sensitivity analysis indicated that the most influential parameters in the model for both the Applicant and the NCPE adjusted base case related to recurrence rates for linzagolix and comparator treatments, followed by the relative effect of linzagolix versus GnRH agonists in the surgical subpopulation, as well as post-surgery utility values and the time to treatment discontinuation rates in both subpopulations.

A Price-ICER analysis was conducted to estimate the reductions in the PtW of linzagolix (expressed as a total rebate on the PtW) which would be required for linzagolix to meet the €45,000/QALY and €20,000/QALY thresholds.

Table 4: Results of Price-ICER analysis (on the NCPE adjusted base case) [a]

	Surgical subpopulation (vs GnRH agonists)	Long-term subpopulation (vs BSC)
ICER	**Reduction in linzagolix PtW**	
€45,000/QALY	49%	32%
€20,000/QALY	85%	Cannot be reached

BSC: best supportive care; **GnRH:** gonadotropin-releasing hormone; **ICER:** incremental cost-effectiveness ratio; **PtW:** price-to-wholesaler; **QALY:** quality adjusted life year;

[a] Expressed as a total rebate (inclusive of the Framework Agreement Rebate of 9%)

4. Budget impact of linzagolix

The price to wholesaler of one pack of linzagolix 100mg or 200mg tablets (pack size: 28) is €92. The mean cost per patient per treatment course in the surgical subpopulation was estimated as €2,234 and €3,232 in the Applicant and NCPE adjusted base cases, respectively. The mean cost per patient per treatment course in the long-term subpopulation was estimated as €8,146 and €6,583 in the Applicant and NCPE adjusted base cases, respectively. As packs are flat-priced the linzagolix 100mg packs should not be used to achieve a dose of 200mg once daily as otherwise the cost per patient will double.

Based on clinical opinion, the Applicant assumes that approximately 30% of the patients in the budget impact model are intended for surgery with the remainder on long-term pharmacological treatment. GnRH agonists were included as comparators for those patients intended for surgery.

The Applicant assumed 10% of the eligible population would receive linzagolix in Year 1 increasing to 30% by Year 5. Consequently, in the budget impact model 538 patients are treated with linzagolix in Year 1 increasing to 1,696 by Year 5. The market share projections provided by the Applicant are associated with inherent uncertainty and appear low particularly for patients on long-term treatment in the second-line setting for whom the comparator is BSC. The Applicant applied an annual discontinuation rate (14.33%) for linzagolix based on the PRIMROSE trials. Based on the aforementioned assumptions, the Applicant estimates the five-year cumulative gross and net budget impacts to be €8.93 million and €7.33 million, respectively.

Results of the cost-effectiveness analysis and budget impact analysis are made under the assumption that patients on the 200mg once daily dose are dispensed the 200mg tablets (rather than the 100mg tablets).

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment

6. Conclusion

The NCPE recommends that linzagolix (Yselty) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

The HSE may wish to manage the prescribing of linzagolix due to the uncertainty associated with an added benefit over GnRH agonists in patients intended for surgery. Furthermore, linzagolix is also licensed for the treatment of endometriosis which has not been assessed by the NCPE.

*Next steps: The NCPE Assessment Report and recommendation will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.
Further information on this process may be found here.