Linzagolix for treating moderate to severe symptoms of uterine fibroids [ID6190] – ACM2

Slides for projector – confidential information is redacted

Technology appraisal committee C 4th June 2024

Chair: Steve O'Brien

External assessment group: SHTAC

Technical team: Luke Cowie, Ellie Donegan, Ian Watson

Company: Theramex

Linzagolix for treating moderate to severe symptoms of uterine fibroids

- ✓ **Recap**
- ❑ New company evidence & analysis*

* Company provided updates to the cost effectiveness modelling for populations 1 and 2, an updated ITC, results of an expert elicitation panel, and comments on the draft guidance.

No other consultation responses to the draft guidance were received.

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Committee's key conclusions from first committee meeting

Linzagolix is recommended only when it is used longer-term without ABT, and at a dosage of 200 mg once daily up to 6 months followed by 100 mg once daily.

Populations 1 and 2: Cost comparison approach not appropriate for decision making: company NMAs did not show similar health benefits for linzagolix and relugolix CT, and were highly uncertain. So linzagolix not recommended in these populations. Need to see results of cost-utility analyses.

Population 3: Cost-utility analysis deemed appropriate, and linzagolix recommended in this population. Preferred economic model assumptions:

- **Utilities:** Use of EQ-5D may not accurately capture QoL, use of UFS-QoL is appropriate.
- **Resource use:** Both company and EAG resource costs appropriate for decision making, with removal of annual GP monitoring costs.
- **Components of BSC:** Minor differences between EAG and company definitions of BSC have a very small impact on cost-effectiveness.
- **Distribution of surgery:** Conflicting estimates on the distribution of different surgeries in the company's 3 populations not expected to have a big impact on cost-effectiveness.

Abbreviations: NMA, network meta-analysis; EQ-5D, EuroQol five Dimension questionnaire; UFS-QoL, Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire; QoL, quality of life; BSC, best supportive care

Population subgroups summary

Population 1	Population 2	Population 3
• Linzagolix for 6 months or less (e.g waiting for surgery) • Company estimates [redacted] of UK patients have surgery and [redacted] of patients treated with the aim of reducing fibroid volume short term had a GnRH antagonist	• Linzagolix with ABT longer term (may or may not have surgery) • Company estimates [redacted] of UK patients have long-term pharmacological treatment	• Add back therapy not suitable. Linzagolix alone longer term (may or may not have surgery) • Company market research estimates [redacted] and [redacted] of UK patients contraindicated to or would prefer not to have ABT
• Intervention: 200mg linzagolix without ABT	• Intervention: Linzagolix 200mg with ABT	• Intervention: Linzagolix only, 200mg for 6 months followed by 100mg
• Comparators: relugolix CT (GnRH antagonist), GnRH agonists*	• Comparators: relugolix CT	• Comparators: BSC

Currently recommended?

	Population 1	Population 2	Population 3
Linzagolix	No	No	Yes
Relugolix CT	Yes	Yes	N/A

* At ACM1 company included GnRH agonists as a comparator for population 1 cost comparison. These are excluded in company's new cost-utility analysis.

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Abbreviations: GnRH, gonadotropin releasing hormone; ABT, add back therapy; CCA, cost-comparison analysis; CUA, cost-utility analysis; BSC, best supportive care

Comparators in company's new cost-utility analysis

Company have excluded GnRH agonists as a comparator in population 1

Committee conclusion at ACM1

- Relugolix CT and GnRH agonists (leuprorelin, goserelin and triptorelin) are relevant comparators for population 1.

Company

- Have not included GnRH agonists in their new cost-utility analysis for population 1.
- Claim that for patients receiving short-term treatment of 6 months or less the most relevant comparator is relugolix CT, based on the recommendations in NICE TA832.
- GnRH agonists also licensed in the short-term setting, but TA832 concluded that relugolix CT is similarly effective to GnRH agonists.
- NICE draft guidance references clinical opinion that many patients likely to receive relugolix CT instead of GnRH agonists, because of ease associated with oral administration.

EAG comments

- EAG does not agree with exclusion of GnRH agonists as comparator for population 1. Company rationale (TA832 concluded that relugolix CT is similarly effective to GnRH agonists) is not convincing.
- Exclusion of GnRH agonists is inconsistent with approach taken in original company submission.

Is relugolix CT the most relevant/only comparator for the cost-utility analysis of population 1?

Abbreviations: ACM1, first appraisal committee meeting; GnRH, gonadotropin-releasing hormone; CT, combination therapy;

Linzagolix (Yselty, Theramex)

Technology details

Marketing authorisation	• "Treatment of moderate to severe symptoms of Uterine Fibroids in adult women of reproductive age" – Granted 14/06/2022
Mechanism of action	• GnRH antagonist which mediates a dose dependent reduction in serum estradiol and progesterone. This may reduce symptoms and size of uterine fibroids.
Administration	• Oral tablet taken once daily. • Four dosing regimens available, 100mg and 200mg with or without add back therapy. Selected based on individual's needs • ABT is estradiol 1mg and norethisterone acetate 0.5mg (once daily additional tablet)
Price	• [redacted] per 28-pack of 100mg or 200mg tablets, £13.20 per 84 pack of ABT tablets • List price for 12 months of treatment is [redacted] (no ABT) or [redacted] (with ABT) • A confidential patient access scheme applies to Linzagolix.

Abbreviations: ABT, hormone add back therapy; GnRH, GnRH, gonadotropin-releasing hormone

Linzagolix for treating moderate to severe symptoms of uterine fibroids

- ❑ Recap
- ✓ **New company evidence & analysis**

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Key issue: New cost-utility analysis (1)

Company's new cost-utility analysis for linzagolix v relugolix CT

Committee conclusion at ACM1

- Cost-comparison methodology (populations 1 and 2) was not suitable for decision making, so company should provide cost-utility analyses, incorporating various outcomes, for these populations.

Company

- Same economic model as used for population 3 in company's original submission, but using EAG base case preferred assumptions. Model also captures effects of treatments on fibroid size through different distribution of surgery types (base case) and associated utility increment for linzagolix (scenario).
- Linzagolix and relugolix CT efficacy incorporated into model using naïve comparison in base case (response outcome from LIBERTY/PRIMROSE trials); fixed/random effects NMAs provided as scenarios (very uncertain).
  - Some trial differences in patient characteristics at baseline, methods used to measure MBL (sanitary product collection being more burdensome in PRIMROSE), and how missing data were handled.
  - These differences suggest that outcomes from a NMA for MBL are a conservative estimate of the relative effectiveness of linzagolix versus relugolix CT.
  - Given these factors, placebo effect observed in PRIMROSE (not expected in clinical practice), and substantial limitations with NMA, naïve comparison of response rates considered appropriate for base case.

EAG comments

- Model is appropriate: Markov model with 6 health states based on controlled and uncontrolled symptoms, surgery and menopause; symptom control based on heavy menstrual bleeding response at 24 weeks (MBL <80ml and >50% reduction vs baseline) Company's model overview from ACM1

Abbreviations: NMA, network meta-analysis; CT, combination therapy; MBL, menstrual blood loss

Key issue: New cost-utility analysis (2)

Company's new cost-utility analysis for linzagolix v relugolix CT

EAG comments

- EAG do not agree with the use of a naïve comparison of response outcome, because it does not account for trial heterogeneity of MBL assessment methods, or difference in placebo response (assumes no placebo effect). It also does not account for differences in baseline characteristics.
- Company also did NMA (used in scenario analysis) and anchored MAIC analyses (not used). MAICs have similar limitations, but an unanchored MAIC would have been preferable, subject to adequate matching of baseline characteristics.
- Company's MAIC results achieved reasonably successful matching of the trial baseline characteristics, with no very high weights required, but have not been used in the analysis.
- Odds ratios with credible intervals reported, but credible intervals not used in company's NMA scenarios, so uncertainty in response outcome not considered.

Does the committee consider that the new cost-utility analysis is appropriate for decision making?

- Is the economic model appropriate and does it capture all relevant outcomes?
- Which source of effectiveness estimates (naïve, NMA, MAIC) is most appropriate?

Abbreviations: MBL, menstrual blood loss; CT, combination therapy; MAIC, matching adjusted indirect comparison; NMA, network meta-analysis

Key issue: New cost-utility analysis (3)

Naïve comparison of linzagolix v relugolix CT MBL response rates

- Two outcomes used as inputs for the cost-utility analysis:
  - MBL response rate is the key clinical efficacy outcome used in the company's base case (<80ml / >50% reduction from baseline, using naïve results from LIBERTY 1 and 2 and PRIMROSE 1 and 2)
  - Relative percentage change in primary fibroid volume from company NMA informs utility calculations in scenario analyses (scenarios with 0.03 utility increment in the linzagolix arm improve ICERs for populations 1 and 2 substantially).

Comparing MBL response at 24-weeks LIBERTY 1 & 2 and PRIMROSE 1 & 2

Treatment arm	Trial	24-week response	28-day cycle probability
Linzagolix 100mg	PRIMROSE 1 & 2	56. 5%	13.0%
Linzagolix 100mg + ABT	PRIMROSE 1 & 2	71.6%	18.9%
Linzagolix 200 mg	PRIMROSE 1 & 2	74.5%	20.4%
Linzagolix 200 mg + ABT	PRIMROSE 1 & 2	84.5%	26.7%
Placebo	PRIMROSE 1 & 2	32.2%	6.3%
Relugolix CT	LIBERTY 1 & 2	72.3%	19.3%
Placebo	LIBERTY 1 & 2	16.8%	3.0%

Abbreviations: CT, combination therapy; ITC, indirect treatment comparison; MBL, menstrual blood loss

Key issue: New cost-utility analysis (4)

Corrected NMAs for linzagolix v relugolix CT for MBL outcome

Updated NMA results: OR of MBL response, relugolix CT versus linzagolix doses

Comparison, relugolix CT versus	OR*	CrI
Fixed-effects NMA		
Linzagolix 100mg	[redacted]	[redacted]
Linzagolix 100mg + ABT	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]
Random-effects NMA		
Linzagolix 100mg	[redacted]	[redacted]
Linzagolix 100mg + ABT	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]

* OR > 1 favours relugolix CT, but wide credible intervals indicate high uncertainty of results

Company comments

- Error identified in data imputed into NMA, impacting results of comparison for the response (MBL) endpoint.
- All other NMAs provided in original company submission remain unaffected (including % change in MBL, pain, fibroid volume, haemoglobin percentage change, UFS-QoL). Of these, only fibroid volume used in model.

NMA results slide from ACM1

Abbreviations: OR, odds ratio; CrI, credible interval; ABT, add-back therapy; NMA, network meta-analysis; MBL, menstrual blood loss; UFS-QoL, Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire

Key issue: Uncertain distribution of surgery types

Company's new expert elicitation from 10 UK clinical experts

Committee conclusion at ACM1

- Conflicting reports on distribution of surgery types was uncertain and may depend on location of clinical practice.

Company

- Expert elicitation with 10 UK clinicians (8 responses).
- Questions asked about the distribution of surgical procedures in current clinical practice, and impact of reduction of fibroid size on this distribution, and requirements for follow on surgeries.
- Results should be interpreted with caution, but the results on distribution of surgeries considered robust.
- Large clinical variation: choice of surgery type is patient-specific, with fibroid size and desire to preserve fertility being important factors. Other factors include surgeon specialty and availability of surgical equipment.
- General consensus that additional [redacted] reduction in fibroid volume (linzagolix 200mg without ABT vs relugolix CT) would lead to shift from open/abdominal to laparoscopic/less invasive procedures, and better surgical outcomes.
- Reduction in fibroid volume with linzagolix 200mg with ABT is [redacted], which is also expected to have an impact.
- Treatment-specific surgery distributions now used in company base case analysis.
- 2 additional surgery types, transvaginal resection and Sonata, now included in economic model for completeness.

EAG comments

- EAG was unable to verify company's expert elicitation results with its own clinical expert.

Is it appropriate to assume treatment-specific surgery distributions?

Abbreviations: ABT, add-back therapy; CT, combination therapy

Base case results – Populations 1 and 2

Company deterministic/probabilistic results – population 1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£2,726
Probabilistic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£3,408

Company deterministic/probabilistic results – population 2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg + ABT	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£5,524
Probabilistic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg + ABT	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£6,001

Abbreviations: ICER, incremental cost effectiveness ratio; NHB, net health benefit; LYG, life years gained; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; CT, combination therapy; ABT, add-back therapy

Scenario analyses (1)

Alternative response rates from NMA and MAICs have biggest ICER impact

EAG conducted a range of exploratory scenario analyses for populations 1 and 2, covering baseline characteristics, treatment discontinuation, surgery utilities and NMA and MAIC odds radios:

- using alternative response rates obtained from the NMA and MAICs had the biggest impact on overall cost-effectiveness results, with the ICER for linzagolix vs relugolix CT ranging from £37,485 per QALY to linzagolix being dominated (more expensive and less effective).
- For remaining scenarios, ICER for linzagolix compared to relugolix CT remained below £20,000 per QALY.

EAG also reproduced the company's scenario analyses where the efficacy for relugolix CT versus linzagolix is informed by fixed- and random-effects NMAs:

- all scenarios except those concerning the utility increment for fibroid reduction resulted in linzagolix being strictly dominated (more expensive and less effective) in comparison with relugolix CT.
- For the fibroid shrinkage scenarios, the ICER remained under £20,000 per QALY in both populations.

Abbreviations: NMA, network meta-analysis, MAIC, matching adjusted indirect comparison; ICER, incremental cost-effectiveness ratio; CT, combination therapy;

Scenario analyses (2)

Scenario analyses - Population 1

Scenarios	Incr costs (£)	Incr QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	£2,726
Effectiveness: Fixed-effects NMA	[redacted]	[redacted]	Strictly dominated
Effectiveness: Random-effects NMA	[redacted]	[redacted]	Strictly dominated
Effectiveness: MAIC	[redacted]	[redacted]	Strictly dominated
Surgery distribution: treatment independent	[redacted]	[redacted]	£18,017
Fibroid size: utility increment (pre surgery)	[redacted]	[redacted]	£306

Scenario analyses - Population 2

Scenarios	Incr costs (£)	Incr QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	£5,524
Effectiveness: Fixed-effects NMA	[redacted]	[redacted]	Strictly dominated
Effectiveness: Random-effects NMA	[redacted]	[redacted]	Strictly dominated
Effectiveness: MAIC	[redacted]	[redacted]	Strictly dominated
Surgery distribution: treatment independent	[redacted]	[redacted]	£8,818
Fibroid size: utility increment (pre surgery)	[redacted]	[redacted]	£2,260

Abbreviations: NMA, network meta-analysis, MAIC, matching adjusted indirect comparison; ICER, incremental cost-effectiveness ratio; CT, combination therapy; QALY, quality-adjusted life year

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Thank you.

Backup slides follow

Back-up slides

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Key issue: Uncertain distribution of surgery types (1)

Company's new expert elicitation from 10 UK clinical experts

Distribution of surgery type for first surgery in current clinical practice

	Distribution of surgery type used for the treatment of UFs in current clinical practice (n=8)
Surgery Type	Mean
Uterine artery embolisation	[redacted]
Endometrial ablation	[redacted]
MRI guided focused ultrasound surgery	[redacted]
Myomectomy (open/abdominal)	[redacted]
Myomectomy (laparoscopic)	[redacted]
Hysterectomy (open/abdominal)	[redacted]
Hysterectomy (laparoscopic)	[redacted]
Transvaginal resection	[redacted]
Radiofrequency fibroid ablation	[redacted]
Sonata	[redacted]

- Company considers results of the expert elicitation to be the most appropriate and up-to-date data on distribution of surgeries.
- Better than data used in TA832, that were derived from several literature sources and not UK specific.

Abbreviations: UF, uterine fibroid

Key issue: Uncertain distribution of surgery types (2)

Company's new expert elicitation from 10 UK clinical experts

Impact of pharmaceutical treatment on distribution of surgery type

	Distribution of surgery type after treatment with: (n=8)		
Surgery type	1. Relugolix CT	2. Linzagolix 200mg without ABT	3. Linzagolix 200mg with ABT
	10-[redacted] reduction in primary fibroid volume vs placebo, 24 weeks	+[redacted] extra reduction in primary fibroid volume vs relugolix CT	+[redacted] extra reduction in primary fibroid volume vs relugolix CT
Uterine artery embolisation	[redacted]	[redacted]	[redacted]
Endometrial ablation	[redacted]	[redacted]	[redacted]
MRI guided focused ultrasound surgery	[redacted]	[redacted]	[redacted]
Myomectomy (open/abdominal)	[redacted]	[redacted]	[redacted]
Myomectomy (laparoscopic)	[redacted]	[redacted]	[redacted]
Hysterectomy (open/abdominal)	[redacted]	[redacted]	[redacted]
Hysterectomy (laparoscopic)	[redacted]	[redacted]	[redacted]
Transvaginal resection	[redacted]	[redacted]	[redacted]
Radiofrequency fibroid ablation	[redacted]	[redacted]	[redacted]
Sonata	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CT, combination therapy

EAG exploratory scenario analyses – Population 1

Alternative response rates from NMA and MAICs have biggest ICER impact

	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Company base case	Relugolix CT	[redacted]	[redacted]	£2,726
	Linzagolix	[redacted]	[redacted]	
Response rates (using ORs from NMAs and MAICs)				
Fixed-effects NMA: lower CrI	Relugolix CT	[redacted]	[redacted]	£37,485
	Linzagolix	[redacted]	[redacted]	
Fixed-effects NMA: upper CrI	Relugolix CT	[redacted]	[redacted]	-£905
	Linzagolix	[redacted]	[redacted]	(dominated)
Random-effects NMA: lower CrI	Relugolix CT	[redacted]	[redacted]	£86
	Linzagolix	[redacted]	[redacted]	
Random-effects NMA: upper CrI	Relugolix CT	[redacted]	[redacted]	-£481
	Linzagolix	[redacted]	[redacted]	(dominated)
MAIC	Relugolix CT	[redacted]	[redacted]	-£1,723
	Linzagolix	[redacted]	[redacted]	(dominated)
MAIC: lower CrI	Relugolix CT	[redacted]	[redacted]	£5,814
	Linzagolix	[redacted]	[redacted]	
MAIC: upper CrI	Relugolix CT	[redacted]	[redacted]	-£928
	Linzagolix	[redacted]	[redacted]	(dominated)

Abbreviations: NMA, network meta-analysis, MAIC, matching adjusted indirect comparison; ICER, incremental cost-effectiveness ratio; CT, combination therapy; CrI, credible interval; QALY, quality adjusted life year

EAG exploratory scenario analyses – Population 2

Alternative response rates from NMA and MAICs have biggest ICER impact

	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Company base case	Relugolix CT	[redacted]	[redacted]	£5, 524
	Linzagolix	[redacted]	[redacted]	
Response rates (using ORs from NMAs and MAICs)				
Fixed-effects NMA: lower CrI	Relugolix CT	[redacted]	[redacted]	£8,781
	Linzagolix	[redacted]	[redacted]	
Fixed-effects NMA: upper CrI	Relugolix CT	[redacted]	[redacted]	-£7,140
	Linzagolix	[redacted]	[redacted]	(dominated)
Random-effects NMA: lower CrI	Relugolix CT	[redacted]	[redacted]	£385
	Linzagolix	[redacted]	[redacted]	
Random-effects NMA: upper CrI	Relugolix CT	[redacted]	[redacted]	-£2,904
	Linzagolix	[redacted]	[redacted]	(dominated)
MAIC	Relugolix CT	[redacted]	[redacted]	-£19,298
	Linzagolix	[redacted]	[redacted]	(dominated)
MAIC: lower CrI	Relugolix CT	[redacted]	[redacted]	£9,353
	Linzagolix	[redacted]	[redacted]	
MAIC: upper CrI	Relugolix CT	[redacted]	[redacted]	-£6,505
	Linzagolix	[redacted]	[redacted]	(dominated)

Abbreviations: NMA, network meta-analysis, MAIC, matching adjusted indirect comparison; ICER, incremental cost-effectiveness ratio; CT, combination therapy; CrI, credible interval; QALY, quality adjusted life year

ACM1 slides

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Linzagolix for treating moderate to severe symptoms of uterine fibroids

Technology appraisal committee C [09 January 2024]

Chair: Stephen O'Brien

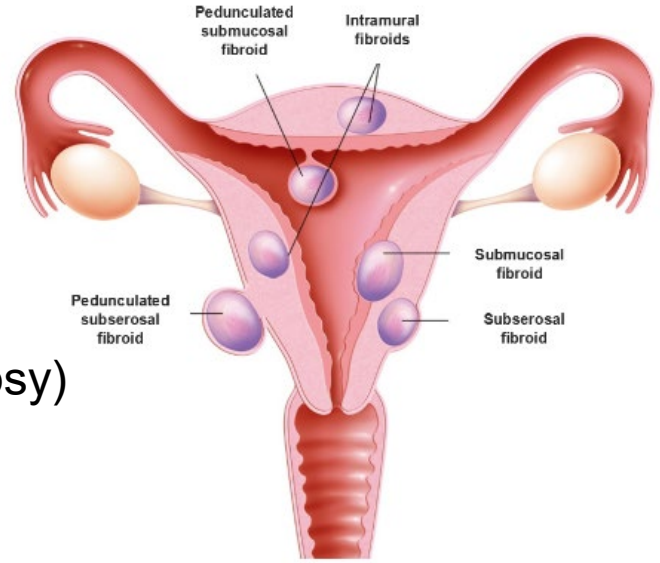
Lead team: Michael Chambers, Ugochi Nwulu

External assessment group: Southampton Health Technology Assessments Centre

Technical team: Samuel Slayen, Eleanor Donegan, Ian Watson

Company: Theramex

Background on uterine fibroids



Diagnosis and classification

- Uterine fibroids common but often too small to cause symptoms
- In symptomatic people diagnosis confirmed by ultrasound scan (possibly with biopsy)

Epidemiology

- ~66% of women develop at least one uterine fibroid during their lifetime
- UK incidence estimated at 5.8 per 1,000 woman-years and prevalence estimated at 4.5% of those aged 15 to 49
- Risk factors include age up to menopause, vitamin D deficiency, family history, nulliparity and having Black African ethnicity

Symptoms, prognosis and treatment types

- 25-30% of people with uterine fibroids experience moderate to severe symptoms
- Moderate to severe symptoms include pain, heavy menstrual bleeding (HMB) potentially leading to anaemia and reproductive dysfunction
- Pharmacological treatments include GnRH analogues, comprising GnRH agonists (overstimulate GnRH receptors resulting in later desensitisation) and GnRH antagonists (which bind and block those receptors)
- GnRH antagonists may use hormonal add back therapy to reduce adverse effects (e.g bone mineral density loss)

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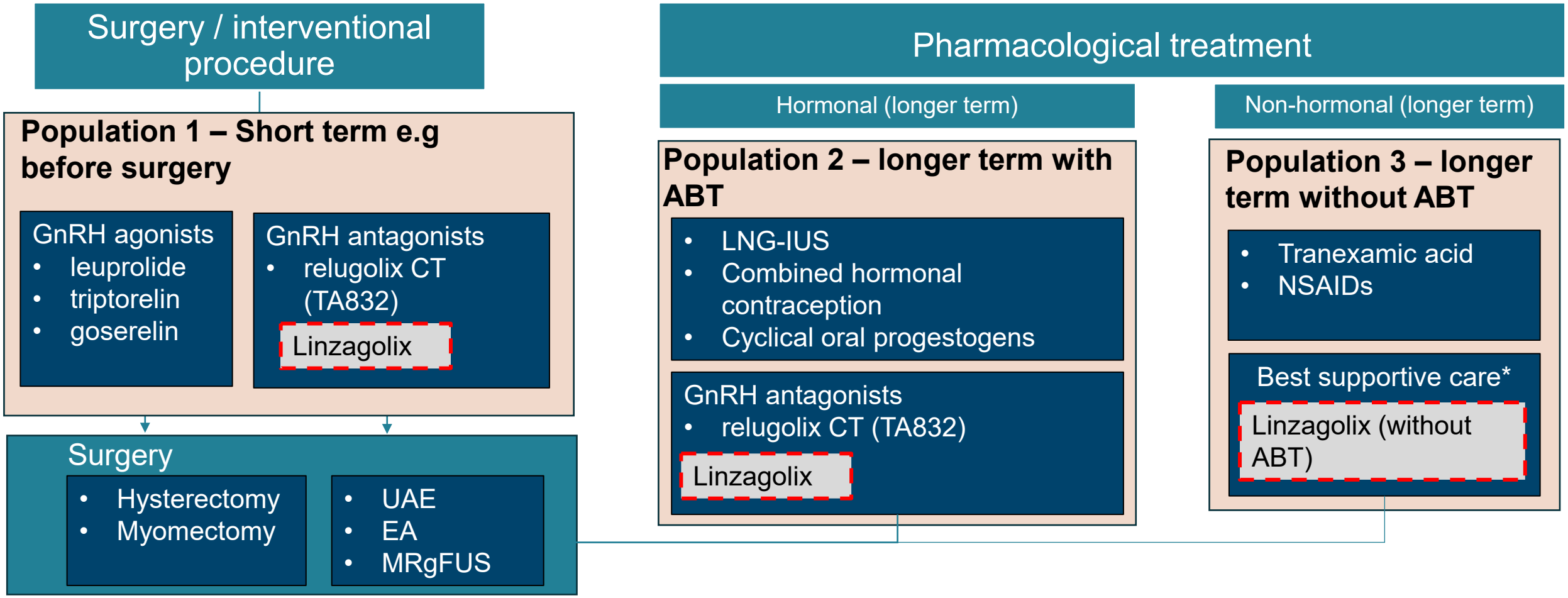
Abbreviations: GnRH, gonadotropin releasing hormones

Treatment pathway

Moderate to severe symptoms of uterine fibroids



Abbreviations: GnRH, gonadotropin releasing hormone; UAE, uterine artery embolization; EA, endometrial ablation; MRgFUS, magnetic resonance guided focused ultrasound; LNG-IUS, levonorgestrel intrauterine system; NSAID, non-steroidal anti-inflammatory drug; ABT, add back therapy; CT, combination therapy

*Diagram reproduced from company submission Figure 5 which is based upon NG88 and TA832

Patient perspectives

No submissions were received from patient organisations for this appraisal. Key points from the patient organisation submission for TA832 (relugolix CT) are presented below.

Fibroid Embolisation: Information, Support, Advice (FEmISA)

Current treatment limitations:

- Treatment of symptomatic fibroids used for short-term before hospital treatment
- Ulipristal acetate withdrawn due to unacceptable side effects and liver failure association
- Hysterectomy and endometrial ablation not options for women wishing to preserve fertility

Unmet need

- A non-invasive, safe and effective treatment associated with low morbidity and mortality and that preserves fertility, sexual function, with minimal side effects and ability to return to work and normal life quickly

Long term effectiveness and safety (TA832 Appeal) – The recommendation from TA832 was appealed by FEmISA

- FEmISA raised concerns that the clinical effectiveness and safety evidence was only available for 1 year but the FAD stated that it could be used long term in line with the marketing authorisation

- A second appeal point was that the FAD stated that relugolix CT preserved the uterus and fertility however there was no evidence of any preservation of fertility by relugolix CT.

Abbreviations: GnRH, gonadotropin releasing hormone; FAD, final appraisal document; CT, combination therapy

Clinical perspectives

Clinically meaningful response

- Amelioration of patients symptoms and improvement of quality of life
- In some cases this would include decrease in fibroid size and prevention of regrowth

Unmet need, innovation and benefits

- Therapies that reduce symptoms with minimal adverse effects and that are amenable to individualised medicine needed
- Different linzagolix regimens beneficial for individualised care and allow titration in response to adverse events or desired effect
- Linzagolix would be more beneficial for those who do not want or cannot have ABT

Longer term efficacy and safety

- 2 year data published for relugolix CT (another GnRH antagonist) showed that 52 week response and safety profile were maintained at 104 weeks.
- Expects that people who would have linzagolix for over 52 weeks would respond in line with the PRIMROSE trials

"As more women become aware that they can have GnRH antagonists without addback with bone preservation with lower doses they may opt for this method of treatment"

Linzagolix offers choice to administer medication on an individualised basis depending on the clinical scenario, response and adverse event profile or a patient. It is thus an innovation above existing therapies

NICE Abbreviations: ABT, add back therapy; GnRH, gonadotropin releasing hormone; CT, combination therapy

Equality considerations

- Black women have an increased risk of developing uterine fibroids, are more likely to have large and multiple fibroids and on average these develop 5-6 years earlier than White women
- Black women also experience higher rates of hospitalisation and surgical intervention compared to White women
- The risk of uterine fibroids increases with age up to menopause
- Linzagolix would be available to everyone with moderate to severe symptoms of uterine fibroids; this may include people who are trans or non-binary
- Clinic visits for treatment with GnRH agonists can result in significant financial and time costs – this could be a particular problem for people from lower socioeconomic groups
- **Clinical expert**: “Black women suffer from lack of equity of access and outcomes when it comes to certain managements for uterine fibroids”

Key issues

Type of issue	Issue	Resolved?	Impact	Analysis
Decision problem and analysis used	Definition of populations in decision problem and appropriateness of type of economic evaluation chosen	No	Large	Both
	Uncertainty around market share of relugolix CT and its use as a comparator in cost-comparison analyses	No	Large	CCA
Evidence on clinical effectiveness	Similar health benefits between linzagolix and GnRH agonists and relugolix CT	No	Large	Both
	Uncertainty around generalisability of PRIMROSE trials	No	Moderate	Both
Cost effectiveness	Uncertainty around post-surgery recurrence of symptoms	Not currently resolvable	Unknown	Both
	Source of data and analysis used to calculate utility values	No	Large	CUA
	Inclusion of vitamin D and calcium in BSC	No	Small	CUA
	Distribution of surgery types	No	Small	Both
	Health resource usage and unit costs	No	Small	CUA
	How discontinuation is modelled (AE only versus all reasons)	Yes	Small	CUA

Abbreviations: CT, combination therapy; GnRH, gonadotropin releasing hormone; BSC, best supportive care; CCA, cost-comparison analysis; CUA, cost-utility analysis; CT, combination therapy

Linzagolix (Yselty, Theramex)

Technology details

Marketing authorisation	• "Treatment of moderate to severe symptoms of Uterine Fibroids in adult women of reproductive age" – Granted 14/06/2022
Mechanism of action	• GnRH antagonist which mediates a dose dependent reduction in serum estradiol and progesterone. This may reduce symptoms and size of uterine fibroids.
Administration	• Oral tablet taken once daily. • Four dosing regimens available, 100mg and 200mg with or without add back therapy. Selected based on individual's needs* • ABT is estradiol 1mg and norethisterone acetate 0.5mg (once daily additional tablet)
Price	• [redacted] per 28-pack of 100mg or 200mg tablets, £13.20 per 84 pack of ABT tablets • List price for 12 months of treatment is [redacted] (no ABT) or [redacted] (with ABT) • A confidential patient access scheme applies to Linzagolix.

***EAG note: It is unclear what proportions of the indicated population correspond to each dose regimen**

 Abbreviations: LH, luteinising hormone; ABT, hormone add back therapy

Population subgroups summary

Population 1	Population 2	Population 3
• Linzagolix for 6 months or less (e.g waiting for surgery) • Company estimates [redacted] of UK patients have surgery and [redacted] of patients treated with the aim of reducing fibroid volume short term had a GnRH antagonist	• Linzagolix with ABT longer term (may or may not have surgery) • Company estimates [redacted] of UK patients have long-term pharmacological treatment	• Add back therapy not suitable. Linzagolix alone longer term (may or may not have surgery) • Company market research estimates [redacted] and [redacted] of UK patients contraindicated to or would prefer not to have ABT
• Intervention: 200mg linzagolix without ABT	• Intervention: Linzagolix 200mg with ABT	• Intervention: Linzagolix only, 200mg for 6 months followed by 100mg
• Comparators: relugolix CT (GnRH antagonist), GnRH agonists	• Comparators: relugolix CT	• Comparators: BSC

EAG:

- Uncertainty around size of population 3 in practice. Clinical expert had not encountered anyone from this group
- Note that neither company submission nor SMPC give criteria for selecting a dose
- Company's market research methodology and relevance to moderate to severe patients is unclear

Is linzagolix positioned in the appropriate populations?
What are the most appropriate comparators for linzagolix in each of the three populations?

Abbreviations: GnRH, gonadotropin releasing hormone; ABT, add back therapy; CCA, cost-comparison analysis; CUA, cost-utility analysis; BSC, best supportive care

Key issue: Comparator market share

Background

- Cost-comparison requires intervention to have similar clinical efficacy to at least one NICE approved comparator

EAG comments [mention tech team considerations if relevant]

- EAG expert estimated 90% of people have GnRH agonists in their practice and relugolix CT uptake is low
- Uncertain if their experts' estimates reflect wider NHS practice
- Company have not provided market share data for the specific population subgroups

Company

- Market research estimates that [redacted] of people using pharmacological treatments for purposes of longer term reduction in uterine fibroid volume in the UK use GnRH antagonists and [redacted] use GnRH agonists.

NICE technical team comments

- NICE cost comparison methods "The chosen comparator must be established in practice and have substantial use in the NHS"

Clinical expert

- All patients who present with anaemia and HMB and awaiting surgery would have relugolix CT (~10-20% of those waiting for hysterectomy or myomectomy) – *Corresponds roughly to Population 1*
- ~20% of people requiring longer term use after no response to first line treatment would have relugolix CT

Are relugolix CT and GnRH agonists appropriate comparators for the cost-comparison analyses for populations 1 and 2?

NICE

Abbreviations: EAG, external assessment group; GnRH, gonadotropin releasing hormone; CT, combination therapy

Clinical effectiveness

- PRIMROSE 1 and 2 trials (double blind RCTs) and their pooled analysis

- PRIMROSE 3, open label off treatment extension trial

NICE National Institute for Health and Care Excellence

Key clinical effectiveness evidence

Clinical trials for linzagolix

- PRIMROSE 1 and 2 trials compare the 4 linzagolix regimens with placebo. Primary outcome is response (reduction in HMB*), various other outcomes measured include change in uterine and fibroid volume.
- Duration 52 wks, key outcomes reported at 24 wks. OLE (PRIMROSE 3) reported some outcomes past 52 weeks.

Other relevant trials – for indirect comparisons

- LIBERTY 1 and 2 trials compare relugolix CT with placebo with a primary outcome of response (reduction in HMB)
- PEARL trials compare leuprolide acetate to placebo. Outcome of reduction in HMB defined differently (PBAC score of less than 75) to PRIMROSE and LIBERTY trials (< 80ml MBL and 50% reduction from baseline, assessed using biochemical AH method)

Indirect treatment comparisons (NMAs and MAICs)

- NMAs were used to compare linzagolix regimens to relugolix CT for: response, % change in MBL, pain improvement, % change in primary fibroid volume, % change in haemoglobin, HRQoL change
- NMAs were provided for the pooled PRIMROSE analysis and for PRIMROSE 1 and 2 separately

- MAICs also used to explore impact of differences in baseline characteristics in PRIMROSE and LIBERTY trials.

- NMAs alone were used to compare linzagolix regimens to leuprolide acetate (GnRH agonist proxy) only possible for three outcomes (response, change in primary fibroid volume and change in haemoglobin from baseline).
  - EAG considered this comparison to be unreliable

Abbreviations: MBL, menstrual blood loss; HMB, heavy menstrual bleeding; OLE, open label extension; AH, alkaline haematin; CT, combination therapy; HRQoL, health related quality of life; CT; combination therapy; NMA, network meta-analysis
*Response defined as ≤80ml reduction in MBL and ≥50% from baseline, assessed using biochemical AH method).

Key issue: Generalisability of clinical trial evidence

Background – Populations in the model were excluded from the PRIMROSE trials

- Population 1: People who would use linzagolix for 6 months or less (e.g whilst waiting for surgery)
- Population 2: People who would use linzagolix longer term (with ABT)
- Population 3: People who would use linzagolix longer term but who can or will not have ABT
- Within trial baseline characteristics similar between arms however differences in ethnicity and BMI between trials

EAG comments

- People in the trials not eligible to have surgery within 6 months (Population 1)
- Maximum trial duration 52 of weeks (some outcomes at 64 weeks) does not fully reflect Population 2
- People contraindicated to ABT excluded from PRIMROSE trials. Company assume patients randomised to the "no ABT" regimens are suitable proxies for contraindicated people. Uncertain if this is valid. (Population 3)
- EAG Clinical expert considered that Population 3 was very small and its relevance to practice uncertain.
- Each trial represents one aspect of NHS clinical practice. PRIMROSE 1 akin to practice in London, PRIMROSE 2 more reflective of EAG expert's own practice in Southampton

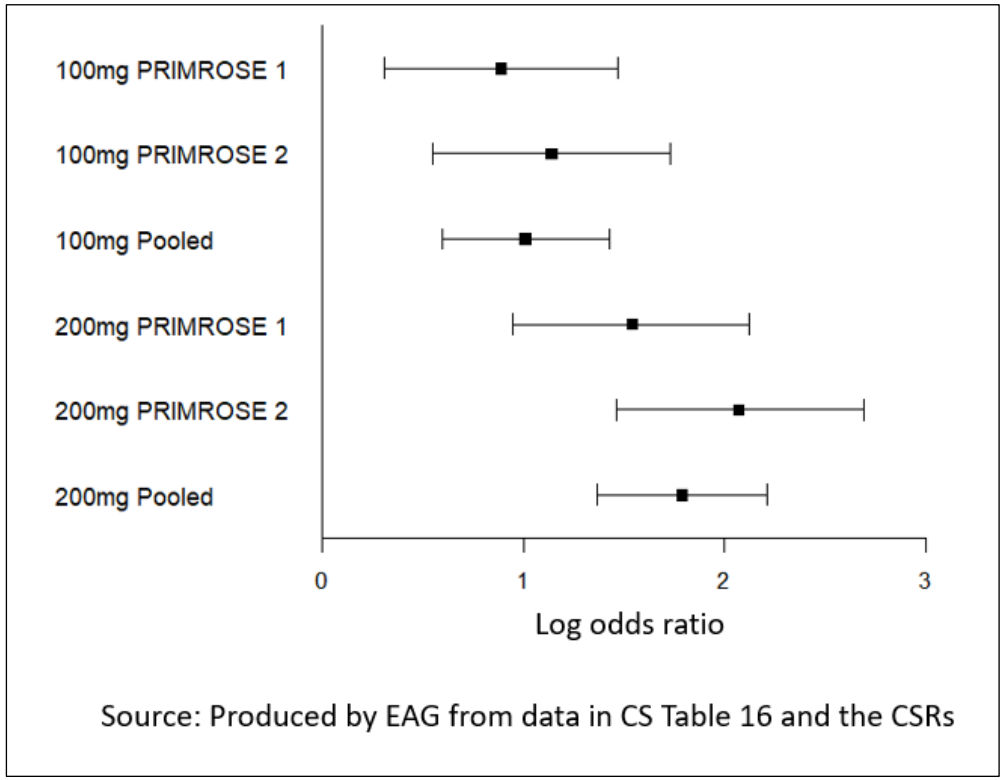
Clinical expert

- Does not expect responses to differ between the PRIMROSE trial populations and the three modelled populations but notes that future studies should investigate this issue
- Combination of PRIMROSE 1 and 2 is reflective of people who have severe uterine fibroid symptoms in the UK

Is the evidence from the PRIMROSE trials generalisable to the clinical practice populations that were modelled and to the population in NHS practice?

Abbreviations: ABT, hormone add back therapy; HMB, heavy menstrual bleeding; EAG, external assessment group

PRIMROSE trials – primary outcome week 24 (reduced HMB)



Source: Produced by EAG from data in CS Table 16 and the CSRs

	Placebo n=205 (%)	100mg n=191 (%)	100mg + ABT n=208 (%)	200mg n=208 (%)	200mg + ABT n=200 (%)
Yes	66 (32.2)	108 (56.5)	149 (71.6)	155 (74.5)	169 (84.5)
No	139 (67.8)	83 (43.5)	59 (28.4)	53 (25.5)	31 (15.5)
OR		2.75	5.54	5.99	10.77
95%CI		1.82; 4.16	3.61; 8.50	3.92; 9.15	6.66; 17.42

- People on linzagolix more likely to respond than placebo (dose response effect)
- Difference between all linzagolix doses and placebo statistically significant at 24 weeks (separate and pooled analysis) which was maintained at week 52 for all groups

- Results suggest a placebo effect which company suggest may be caused by non-compliance with sanitary product collection in trial (which would affect placebo group more as they have higher bleeding)
- EAG acknowledge as speculative and there could be other reasons for effect (e.g. regression to the mean). Notes that placebo effect increases slightly from 24 to 52 weeks
- Linzagolix regimens associated with statistically significant improvements versus placebo in secondary outcomes with exception to EQ-5D-5L (all regimens) and primary and uterine volume (100mg no ABT only) – See backup slide

NICE Abbreviations: EAG, external assessment group; OR, odds ratio; 95%CI, 95% confidence intervals;

Adverse events

- Incidence of TEAEs was slightly higher across the linzagolix regimens compared with placebo
- Most TEAEs were mild or moderate in severity. Serious and severe TEAEs were rare and broadly similar across all groups
- TEAEs leading to permanent discontinuation was low and similar across all groups
- At week 52 fewer TEAEs were reported than at week 24 and most that were reported were mild to moderate in severity.
- Incidence of serious and severe TEAEs was low and incidence lower than at week 24.
- Appears to be a dose-dependent reduction in BMD during the first months of treatment. This was only clinically meaningful for the 200mg (no ABT) dose at 24 weeks. (assuming a ≥5% change would be clinically meaningful)
- **EAG note:** during continued treatment BMD loss was less rapid although it is uncertain whether this pattern would be sustained in the longer term.
- **Clinical expert note**: Publication of longer term (2 year) safety data shows no new adverse events through 104 weeks for relugolix CT.

Is the adverse events evidence from the PRIMROSE trials generalisable to the clinical practice populations that were modelled and to the population in NHS practice?

Abbreviations: TEAE, treatment emergent adverse event; ABT, hormonal add back therapy; BMD, bone mineral density; CT, combination therapy

NMA results – Linzagolix vs relugolix CT – Response (fixed effects)

Fixed effects NMAs for response

Random effects NMA for response (pooled only)

[Please note different X axis scale]

- EAG were unable to verify the NMA code used
- Credible intervals in the fixed and random effects analysis are so wide it is not possible to estimate where the true effect may lie
- Linzagolix 200mg + ABT likely [redacted] to relugolix CT (See clarification response table 13)
- This appears to be driven by large effect in PRIMROSE 2
- relugolix CT is likely [redacted] to all other linzagolix regimens whose credible intervals lie [redacted]
- Similarity of linzagolix and relugolix CT at eliciting response [redacted]
- EAG prefer random effects NMA due to between trial heterogeneity.
- Ideally, non-inferiority analyses would have been pre-specified to inform NMAs and allow conclusion on treatment similarity
- To make a conclusion on clinical similarity with trials powered for superiority analysis would require sufficiently narrow credible intervals

Abbreviations: NMA, network meta-analysis; MAIC, matching adjusted indirect comparison; ABT, hormone add back therapy, ESS effective sample size;

NMA results – Other outcomes summary (linzagolix vs relugolix)

Outcome	Model	Linzagolix 100 mg	Linzagolix 100 mg plus add back therapy	Linzagolix 200 mg	Linzagolix 200 mg plus add back therapy
Response	Fixed effects				
Response	Random effects				
% change in menstrual blood loss	Fixed effects				
% change in in menstrual blood loss	Random effects				
Pain	Fixed effects				
Pain	Random effects				
% change in primary fibroid volume	Fixed effects				
% change in primary fibroid volume	Random effects				
% change in haemoglobin	Fixed effects				
% change in haemoglobin	Random effects				
Change in uterine fibroid symptom quality of life score	Fixed effects				
Change in uterine fibroid symptom quality of life score	Random effects				

Please see backup slides 36 to 40 for details

Key issue: Similar health benefits (Pop. 1 and 2)

Unclear if the analyses show that linzagolix is clinically similar to comparators

Background

- Cost-comparison methodology (populations 1 and 2), requires similar clinical efficacy between linzagolix and comparators, which is uncertain

Company

- Prefer fixed effects NMAs with have credible intervals that do not indicate a difference in efficacy between most linzagolix regimens and relugolix CT for most outcomes.

EAG comments

- EAG prefers random effects NMAs (greater accounting of heterogeneity, which appears to be present)
- 200mg without ABT (population 1) statistically [redacted] only for reduction in primary fibroid volume
- 200mg + ABT appears to have [redacted] efficacy against relugolix CT (response and reduction in fibroid volume)
- Company appears to assume that statistical non-significance equals similarity in clinical efficacy
- Conclusions on clinical similarity are difficult to make due to the wide credible intervals for many NMAs
- Clinical similarity between linzagolix regimens and relugolix CT does not appear to be supported for key outcomes
- NMAs for linzagolix versus leuprolide acetate hard to interpret due to lack of reporting and are of limited use

Does the committee consider that linzagolix is clinically similar to relugolix CT and GnRH agonists?

Abbreviations: GnRH, gonadotropin releasing hormone; CT, combination therapy

Cost effectiveness

Cost-comparison model for populations 1 and 2

Cost utility model for population 3

NICE National Institute for Health and Care Excellence

Company's model overview

Populations 1 & 2 cost-comparison

- Four states, on/off treatment, menopause, death
- 28-day cycle
- Costs included: drug, administration, healthcare resource use and surgery
- 45.1% of people assumed to have surgery, applied as a one of cost in cycle 0.

Population 1 (200mg, no ABT)

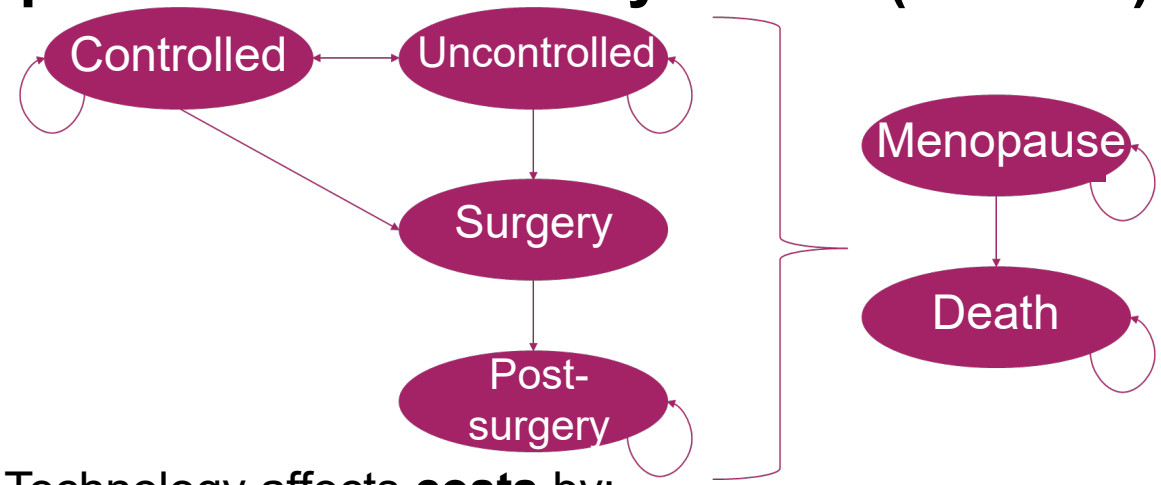
- Time horizon: 6 months
- No clinical efficacy parameters included, everyone is on treatment for 6 months

Population 2 (200mg, with ABT)

- Treatment discontinuation rate of [redacted] discontinuation from PRIMROSE trials was converted to [redacted] per cycle in the model
- Menopause and general mortality modelled from literature estimates
- No treatment or surgery after menopause

Abbreviations: QALY, quality adjusted life year; UFS-QoL, uterine fibroids symptoms and quality of life score; PSS, prescribed specialist services

Population 3 cost-utility model (no ABT)



- Technology affects **costs** by:
  - Accruing drug and health state resource costs
  - Rates of surgery and distribution of types
- Technology affects **QALYs** by:
  - Affecting transition through health states and associated utility (and adverse event incidence)
    - Transition probabilities derived from 24 week clinical trial results
  - Reducing overall probability of surgery
  - Changing distribution of surgery
- Assumptions with greatest ICER effect:
  - Recurrence rate and treatment withdrawal rates
  - Choice of HRQoL data (EQ-5D-5L vs UFS-QoL)

Key issue: Utilities (Population 3 only)

Background

- PRIMROSE 1 & 2 trials collected QoL data using UFS-QoL and EQ-5D-5L instruments, (mapped to EQ-5D-3L and using a linear mixed model to estimate utility for controlled and uncontrolled bleeding health states)
- Key driver of cost-effectiveness estimates

Company

- Base case uses UFS-QoL mapped to EQ-5D-3L utility values (controlled [redacted], uncontrolled [redacted],) as the disease-specific UFS-QoL is a more reliable measure to capture QoL in people with uterine fibroids
- Scenarios provided using EQ-5D-5L mapped to EQ-5D-3L (controlled [redacted], uncontrolled [redacted],) and utility estimates from the Hux et al (2015) study (controlled 0.73, uncontrolled 0.55)

EAG comments

- Company's mapping is consistent with TA832 (relugolix CT) where UFS-QoL was mapped to EQ-5D-3L (in the absence of complete EQ-5D-5L data)
- Unable to verify the linear mixed model used to estimate utility. Provide scenarios to explore LMM utility function.
- Using the EQ-5D-5L mapped to EQ-5D-3L scenario increases the total QALYs more for the BSC arm, which decreases the incremental QALYs and raises the linzagolix ICER substantially. (EAG base case)
- Acknowledge company preference for disease specific measures (confirmed by their expert) but also note that NICE reference case prefers EQ-5D data where available.

Do the committee consider the utility estimates mapped from the UFS-QoL or the EQ-5D-5L to be more appropriate?

Abbreviations: QoL, quality of life; UFS-QoL, uterine fibroid severity quality of life score; ICER, incremental cost-effectiveness ratio

Key issue: Post surgery recurrence of symptoms

Background

- The model assumes that once people enter the “post-surgery” state they stay there until moving to the menopause state. This implies that there is no recurrence of symptoms after any surgery type.

EAG comments

- Uncertainty about how the prognosis of different surgery types will vary and whether patients who have surgeries other than hysterectomies might experience recurrence of UF symptoms
- Would have preferred an option in the model to allow modelling of recurrence from the post-surgery state for both arms.

Clinical expert

- Not possible to have zero recurrence after all surgery types. As long as the womb is retained there is a chance of recurrence as fibroids develop from single muscle fibres within the uterus.
- The recurrence of fibroids and symptoms is complex, depending on: type of surgery, number and size of fibroids and the expertise of the surgeon
- As a general rule recurrence is more common after laparoscopic surgery than after open surgery and is least common for hysteroscopic surgery. (People having hysterectomy have no chance of recurrence of symptoms)
- 5-10% of women having surgical interventions for fibroids will need another intervention within 5-10 years (this proportion will fall with increasing age)

NICE

Is it appropriate to assume no recurrence of symptoms of uterine fibroids after surgery?

Costs breakdown (Population 3)

Linzagolix drug costs

- Treatment discontinuation modelled at [redacted], and [redacted] per cycle for 100mg and 200mg of linzagolix respectively and [redacted] per cycle for BSC in both base cases
- At 6 months everyone on linzagolix 200mg moves to the 100mg regimen (see line X on graph)
- Total costs largely driven by high cost of surgery. Incremental costs driven by drug costs of linzagolix.

Analysis	Intervention	Surgery costs	Drug costs	Administration costs	Resource use costs	AE costs	Total
Company	Linzagolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base	Linzagolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
case	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Month	% on treatment
0	[redacted]
6	[redacted]
12	[redacted]
18	[redacted]
24	[redacted]

NICE Abbreviations: BSC, best supportive care; TTD, time to discontinuation

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Source of utilities	PRIMROSE UFS-QoL mapped to EQ-5D-3L	PRIMROSE EQ-5D-5L mapped to EQ-5D-3L
Unit costs	Gynaecologist £185.51, MRI £197.37	Gynaecologist £181.26, MRI £255.41
Medications used for BSC	NSAIDs and iron supplements	Addition of Vitamin D and Calcium
Surgery and HRU	See backup slide	

Clinical expert

- The company surgery numbers are reflective of general clinical practice. However there is published literature that differs from both estimates
- Both scenarios would be appropriate depending on how linzagolix is introduced (hospital only vs shared care with GP). However there are no one year follow ups at present for GnRH antagonists

What are the committee preferred assumptions for each of these parameters?

Abbreviations: NSAID, non-steroidal anti inflammatory drug; BSC, best supportive care; HRU, healthcare resource use
*Company base case as per TA832. EAG base case after consultation with EAG clinical expert.

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Company base case results – Cost comparison

Treatment	Population #1		Population #2	
	Total costs	Incremental costs	Total costs	Incremental costs
Linzagolix	[redacted]	-	[redacted]	-
relugolix CT	£3,411	[redacted]	£4,752	[redacted]
Leuprorelin	£3,441	[redacted]	-	-
Goserelin	£3,407	[redacted]	-	-
Triptorelin	£3,482	[redacted]	-	-

EAG base case results – Cost comparison

Treatment	Population #1		Population #2	
	Total costs	Incremental costs	Total costs	Incremental costs
Linzagolix	[redacted]		[redacted]	-
relugolix CT	£3,417	[redacted]	£4,757	[redacted]
Leuprorelin	£3,446	[redacted]	-	-
Goserelin	£3,413	[redacted]	-	-
Triptorelin	£3,488	[redacted]	-	-

Base case results – Population 3 (200mg no ABT)

Company deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
BSC	[redacted]	[redacted]	-	-	-	-	
Linzagolix 200mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,392	0.02	0.04

EAG deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
BSC	[redacted]	[redacted]					
Linzagolix 200mg	[redacted]	[redacted]	[redacted]	[redacted]	£28,973	-0.017	0.001

EAG notes that company probabilistic results were in line with deterministic ones.

No.	Scenario (applied to company base case)	Δcosts (£)	Δ QALYs	ICER (£/QALY)
1	Include vitamin D and calcium in BSC and EAG surgery distribution	[redacted]	[redacted]	£15,705
2	EAG healthcare resource use and unit costs	[redacted]	[redacted]	£14,478
3	Utilities mapped from EQ-5D-5L	[redacted]	[redacted]	£28,973

Abbreviations: ICER, incremental cost effectiveness ratio; NHB, net health benefit