NICE Technology Appraisals (TA) briefing paper for local implementation

NICE TA Guidance name and number	Linzagolix (Yselty) for the treatment of moderate to severe symptoms of uterine fibroids (NICE TA 996)		
Available at	https://www.nice.org.uk/guidance/ta996		
Date of issue	14 August 2024	**Implementation deadline**	14 November 2024

Medicine details	
Name and brand name	Linzagolix (Yselty)
Manufacturer	Theramex
Mode of action	**www.medicines.org.uk** Linzagolix is a selective, non-peptide gonadotropin-releasing hormone (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.
Licenced indication	**www.medicines.org.uk** Yselty is indicated for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. **Posology** Yselty (linzagolix) should be initiated and supervised by a physician experienced in the diagnosis and treatment of uterine fibroids.
Formulation	Film-coated tablet (100mg & 200mg)
Dosage	**www.nice.org.uk** • with hormonal add-back therapy (ABT): 200 mg once daily • without hormonal ABT: 200 mg once daily for 6 months, then 100 mg once daily. To note: Hormone add-back therapy (ABT) is stated as 'estradiol 1mg and norethisterone acetate 0.5 mg tablet once daily' in the product license.
Comparison of NICE TA with Summary of Product Characteristics (SmPC)	**www.medicines.org.uk** **Note that linzagolix is licensed for short term use (see below) but is not recommended by NICE from a cost effectiveness perspective** • 200 mg once daily for short-term use (< 6 months) in clinical situations when reduction of uterine and fibroid volume is desired (see section 5.1). Fibroid size may increase when the treatment is stopped. Due to the risk of bone mineral density (BMD) decrease with prolonged use, the 200 mg dose without concomitant ABT should not be prescribed for longer than 6 months. This is the current dose considered by NICE as part of this NICE evaluation. Subsequent changes in the licence following NICE publication will need to be considered by the Area Prescribing Committee and will not be routinely funded by local commissioners, as the incremental cost per QALY would not have been considered.

NICE TA recommendations
Recommendations
1. Recommendations 1.1. Linzagolix is recommended as an option for treating moderate to severe symptoms of uterine fibroids in adults of reproductive age only if:

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

1.2. This recommendation is not intended to affect treatment with linzagolix that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

Usual treatment for moderate to severe symptoms of uterine fibroids includes hormonal contraceptives and gonadotropin-releasing hormone (GnRH) receptor agonists and antagonists. GnRH antagonists, such as relugolix combination therapy (CT), may contain hormonal ABT. Other treatments include best supportive care, for example, iron supplements and painkillers.

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

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

Decision making framework (DMF)

National guidance and priorities

The ICS has a legal obligation to commission this medicine in line with the NICE TA.

- This NICE TA has been assigned an implementation deadline of 3 months
- The implementation deadline is 14th November 2024.

Clinical effectiveness

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

Patient safety

- The product should be used in line with recommendations made by NICE.
- ▼ This is a Black Triangle drug – this medicinal product is subject to reporting of all suspected adverse drug reactions to the MHRA. This will allow timely identification of new safety information.

www.medicines.org.uk

- Linzagolix should be avoided in women with moderate (eGFR = 30– 59 mL/min), severe renal impairment (eGFR < 30 mL/min) or end-stage renal disease
- Increases in lipid levels were observed with linzagolix treatment. These increases were generally of no clinical relevance. However, in women with pre-existing elevated lipid profiles monitoring of lipid levels is recommended.
- Patients with known depression or history of depression should be carefully monitored during treatment. Treatment should be discontinued if depression recurs to a serious

degree.

Patient factors

- An additional treatment option would be valued by patients.
- This is an oral treatment
- Convenience for patients
- Potential improved adherence
- Long-term control of symptoms
- Potential non-surgical treatment option
- Linzagolix should preferably be started in the first week of the menstrual cycle and should be taken continuously once daily.
- Pregnancy should be ruled out prior to starting treatment
- In patients with risk factors for osteoporosis or bone loss a DXA scan is recommended prior to starting treatment with linzagolix.
- DXA scan is recommended after 1 year of treatment for all women
- There is a need for continued Bone Mineral Density (BMD) monitoring on an annual basis depending on the prescribed dose of linzagolix.

Environmental impact

- Packaging waste would be additional to usual municipal waste recycling or landfill.
- Discharge into the wastewater system (post-metabolism) from an individual patient is unlikely to have a significant impact short term, however the long-term impact to the water ecosystem is unknown.

Equality & diversity

www.nice.org.uk

Age

- Licensed for moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- Negative impact for patients under 18 years of age with moderate to severe symptoms of uterine fibroids.

Gender reassignment

- People with Uterine Fibroids may be trans. NICE took this into account in its decision making.

Race

- Black women are more likely to have multiple fibroids that are large, so are more likely to need hospitalisation or surgical intervention

Sex

- Heavy menstrual bleeding and uterine fibroids affect women.

Place in therapy relative to available treatments

www.nice.org.uk

The clinical experts explained that one of the benefits of linzagolix is the flexible dosing and the potential to use either dose with or without hormonal ABT.

Treatment pathway

1st line (to reduce symptoms of uterine fibroids)

Treatment to control bleeding (tranexamic acid), pain management (NSAIDs) & oral contraceptives or levonorgestrel intrauterine system (coil).

Subsequent treatment

Gonadotropin-releasing hormone (GnRH) analogues which consist of:

- **GnRH agonists -** Leuprorelin, goserelin and triptorelin, which initially overstimulate GnRH receptors and later downregulate oestrogen and progesterone.

- **GnRH antagonists -** Relugolix combination therapy (CT). These drugs bind and inhibit the GnRH receptor to down regulate oestrogen and progesterone.

Because GnRH antagonists can result in very low oestrogen and progesterone levels,

hormonal add-back therapy (ABT) may be used to reduce any adverse effects of these low levels (including low bone mineral density). This is the case with relugolix combination therapy, in which hormonal ABT (estradiol–norethisterone acetate) is part of the treatment.

Many people are offered surgery or interventional procedures to remove or reduce the size of uterine fibroids. Surgery may include myomectomy or hysterectomy and could be laparoscopic, hysteroscopic or open abdominal surgery.

Interventional procedures may include uterine arterial embolisation, endometrial ablation and MRI-guided focused ultrasound. The treatments which are offered may depend on the specific treatment aims, patient characteristics (for example, comorbidities) and personal preference, which may be to not have hormonal treatments.

Stakeholder views

The paper was sent out for consultation and comments are listed on the front sheet.

Other ICBs traffic light status:
Derbyshire – RED traffic light status

Cost-effectiveness

www.nice.org.uk
The drug cost per Place according to NICE resources does not exceed £100,000.

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

Section 1: cost of the technology

Annual cost per patient (or complete course if shorter)

NICE approved medicine	Pack size/cost per	Annual cost
Linzagolix (Yselty) 100mg & 200mg film coated tablets	28 tablets - £80.00	£1,042 per year (assuming 13 treatment packs required) **Note that if required a patient would also be prescribed hormonal add-back therapy (ABT).**

Availability of CAP/PAS price:

- No.

Price relative to comparable medicines:

GNRH antagonists

Comparators	Pack size/cost per	Annual cost
Relugolix –estradiol-norethisterone (Ryeqo®)	28 tablets - £72.00	£938.57 **Note hormonal add-back therapy (ABT) is included as part of this treatment.**

GNRH agonists (short term use)

Comparators	Pack size/cost per	Annual cost	License (maximum 6 months treatment)
Leuprorelin acetate (Prostap SR DCS®) 3.75mg	Powder and solvent for suspension for injection pre-filled syringes - £75.24	(Every month) £978.12 Calculation made for 28 days treatment for comparison to goserelin	Preoperative management of uterine fibroids to reduce their size and associated bleeding. **Usually for 3-4 months but for a maximum of 6 months**
Goserelin acetate 3.6mg (Zoladex®)	Implant pre-filled syringe £70.00	(every 28 days) £910	In conjunction with iron therapy in the haematological improvement of anaemic patients with fibroids prior to surgery. **May be administered for up to three months before surgery.**
Triptorelin acetate 3mg (Decapeptyl SR®)	Powder and solvent for suspension for injection £69.00	Every 4 weeks for at least 3 months £897	Reduction in size of uterine fibroids **Maximum duration of treatment should be 6 months.**

Section 2: NICE resource impact statement and template

Number of patients Year 1 and Year 5:

Population A

- People receiving long term treatment with hormone-based therapy

Population B

- People receiving long term treatment without hormone-based therapy.

	Current, year 0	year 1	year 2	year 3	year 4	year 5
Population A						
People receiving linzagolix	0	199	401	608	818	1,03
People receiving relugolix	1,968	1,788	1,605	1,418	1,227	1,03
Population B						
People receiving linzagolix	0	27	55	83	112	11
People receiving best supportive care	134	108	82	55	28	2
	2,102	2,122	2,143	2,163	2,184	2,20

The Surrey Heartlands Director of Pharmacy and Medicines Optimisation has delegated authority to enable the Committee to be a decision-making committee providing the impact of any single decision does not exceed £100,000 within an individual Place per annum. Decisions with a cost impact of over £100,000 within an individual Place per annum require authorisation from Surrey Heartlands Health & Care Professionals Committee at their next meeting. Exception to this will be for any decision made in relation to a NICE Technology Appraisal (which are subject to requiring mandatory funding by commissioners) and other urgent items. The exceptions will be taken to the next Executive Meeting (which meets weekly) for authorisation.

Traffic light recommendation to APC

Recommended traffic light status and rationale:

BLUE (on specialist initiation)

- Prescribing initiated and stabilised by specialist but has potential to transfer to primary care WITHOUT a formal shared care agreement.

OR

AMBER

- Prescribing initiated and stabilised by specialist but has potential to transfer to

primary care under a formal shared care agreement.
- BMD monitoring is required on an annual basis according to the licence for linzagolix in all women.

Implementation

Actions to implement

Primary care

- Continue to prescribe treatment as recommended by the specialist team.
- Monitor patient for adverse reactions in women who have mild renal impairment (eGFR = 60-89 mL/min)

Secondary care

- Trusts to follow internal governance procedures to add to their formulary and initiate homecare.
- Specialist teams will be required to arrange a DXA scan prior to treatment in patients with risk factors for osteoporosis.
- DXA scan is recommended after 1 year of treatment for all women and this will be arranged by the specialist team. There is a need for continued Bone Mineral Density (BMD) monitoring on an annual basis depending on the prescribed dose of linzagolix.

ICS

- This technology is commissioned by Surrey Heartlands ICB who are required to comply with the recommendation in the NICE TA within the time set in the publication.

PAD and Joint Formulary

- Established medicines paper for treatments used for managing the symptoms of uterine fibroids will be presented with this briefing paper.
- Patients with fibroids should be managed in line with CKS **https://cks.nice.org.uk/topics/fibroids/management/management/**
- New PAD profile will be required

References:

1 Summary of Product Characteristics. emc. Available at: www.medicines.org.uk Accessed <17/09/2024>

2 NICE Technology Appraisal Guidance: . Available at: www.nice.org.uk/guidance/ta996 Accessed <17/09/2024>

3 NICE Resource Impact Template: . Available at: https://www.nice.org.uk/guidance/ta996/resources Accessed <17/09/2024>

Declaration of interest: None

	Name	Role	Date	Declaration of interests (please give details below)
Prepared by	Clare Johns	Lead Pharmacy Technician (Surrey Heartlands ICB)	17/09.2024	None
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