NHS
Cheshire and Merseyside

Linzagolix for treating moderate to severe symptoms of uterine fibroids (NICE TA996)

AMBER RETAINED - specialist initiation and stabilisation with occasional input to support non-specialist prescribing

Recommendations

The Cheshire and Merseyside Area Prescribing Group recommend linzagolix 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]

Prescribing information

- Linzagolix should be initiated and supervised by a physician experienced in the diagnosis and treatment of uterine fibroids.[2]
- Linzagolix should preferably be started in the first week of the menstrual cycle and should be taken continuously once daily. [2]
- Pharmaceutical form: 100mg and 200mg film-coated tablets. [2]
- The following dosage (for the intended above indications) should be used:
  - with hormonal ABT: 200 mg once daily
  - without hormonal ABT: 200 mg once daily for 6 months, then 100 mg once daily [1]
- Linzagolix can be taken with or without food. [2]
- Pregnancy must be ruled out prior to initiating treatment. [2]
- Any hormonal contraception needs to be stopped prior to initiation.[2]

Implementation notes

Prior to the initiation or reinstitution of linzagolix, a complete medical history (including family history) must be taken. Blood pressure must be measured, and a physical examination must be performed guided by the contraindications and warnings for use. During treatment, periodic check-ups must be carried out according to standard clinical practice. [2]

Treatment should only be initiated by a specialist in the management of uterine fibroids. Prescribing is to be continued by the specialist until stabilisation of the patient's condition is achieved, and the patient has been reviewed by the specialist. The specialist may then request the patient's GP to take over prescribing responsibilities of treatment.

There is no requirement for the specialist to retain prescribing for the first year of treatment, but the patient should remain under the care of the specialist (ie not discharged) during treatment with linzagolix.

Bone Mineral Density (BMD)

In some patients treated with linzagolix, who had normal BMD at start of treatment, BMD loss varying from >3-8% was reported. [2]

In patients with risk factors for osteoporosis or bone loss, a dual X-ray absorptiometry (DXA) scan is recommended prior to starting linzagolix treatment. Linzagolix is contraindicated in osteoporosis. [2]

Monitoring and responsibilities
A DXA scan is recommended after 1 year of treatment for all patients to verify that the patient does not have an unwanted degree of BMD loss. It is the responsibility of the specialist to request the scan and to action the results. [2]

Thereafter, depending on the prescribed dose of linzagolix, further BMD assessment is recommended as below:

- Annually for patients treated with linzagolix 100 mg.
- Frequency should be determined by the treating physician for patients treated with linzagolix 100mg with concomitant ABT and linzagolix 200 mg with concomitant ABT, based on the patient's individual risk and previous BMD assessment. [2]

The specialist is responsible for arranging and actioning any further DXA scans. If the risks of BMD decrease exceed the potential benefit of treatment with linzagolix, treatment should be discontinued. [2] The decision to stop or continue treatment should be clearly communicated by the specialist to the patient's GP after the DXA scan results have been assessed.

The patient should remain under the care of the specialist during treatment with linzagolix.

Patient factors [2]

Lactose - Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Hepatic impairment – Linzagolix should be avoided in severe hepatic impairment (Child-Pugh C). No dose adjustment is necessary in mild or moderate hepatic impairment (Child-Pugh A or B).

Liver enzymes - Asymptomatic transient liver enzyme elevations have been reported. Patients should be instructed to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice. Treatment should be discontinued if jaundice develops. Acute liver test abnormalities may necessitate discontinuation of treatment with linzagolix until liver tests return to normal. In patients with known abnormal hepatic history, a baseline level of hepatic function tests should be obtained, and further regular monitoring should be performed. These patients should be treated with caution.

Renal impairment - Prescribers are recommended to monitor for adverse reactions in mild renal impairment (eGFR = 60-89 mL/min) although no dose adjustment is required. 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.

Cardiovascular disorders/QT prolongation - Linzagolix marginally increases the QT interval but showed no evidence of clinically relevant risk of QT prolongation or Torsade de Pointes. Caution should be exercised in patients who have known cardiovascular disease, family history of QT prolongation or hypokalaemia, and in concomitant use with medicinal products known to prolong the QT interval.

Mood disorders - Mood disorders including depression, alterations in mood, and emotional lability have been observed with treatment with gonadotropin-releasing hormone (GnRH) antagonists including linzagolix. Caution is to be applied in patietns with a history of depression and/or suicidal ideation. 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.

Drug interactions - Linzagolix should be avoided in patients using CYP2C8 sensitive substrate medicinal products with a narrow therapeutic index (e.g. paclitaxel, sorafenib and repaglinide). It is recommended to monitor for increases in adverse reactions associated with other CYP2C8 substrates when co-administered with linzagolix. See SPC for full information.

Contraception - Linzagolix with or without ABT has not been demonstrated to provide contraception. Those of childbearing potential at risk of pregnancy have to use effective non-hormonal contraception while on treatment with linzagolix.

Change in menstrual bleeding pattern and reduced ability to recognise pregnancy – Patients should be informed that treatment with linzagolix usually leads to a significant reduction in menstrual blood loss and often leads to amenorrhoea, which may reduce the ability to recognise the occurrence of a pregnancy in a timely manner. Pregnancy testing should be performed if pregnancy is suspected, and treatment should be discontinued if pregnancy is confirmed.

Pregnancy - There are no or limited amount of data from the use of linzagolix in pregnant women, and use of linzagolix is contraindicated in pregnancy. Studies in animals have shown that exposure to linzagolix early in pregnancy may increase the risk of early pregnancy loss.

Breastfeeding - Linzagolix is contraindicated during breast-feeding. A risk to newborns/infants cannot be excluded.

Safety [2]

Contraindications for linzagolix:

- Hypersensitivity to the active substance or to any of the excipients
- Pregnancy or breast-feeding
- Known osteoporosis
- Genital bleeding of unknown aetiology
- Contraindications related to ABT should be respected if concomitant ABT is given.

The most common adverse reactions reported in the pivotal phase 3 clinical studies 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% of women treated with 100 mg with ABT, 200 mg with ABT, 100 mg and 200 mg, respectively.

Similarly, headaches were reported more frequently at higher doses and decreased with ABT (1.4%, 2.4%, 4% and 6.2% for 100 mg with ABT, 200 mg with ABT, 100 mg and 200 mg, respectively).

Refer to SPC for full safety information.

Cost

Linzagolix

The NHS list price (excluding VAT) of linzagolix is £80 for a 28-pack of 100mg or 200mg tablets.
The cost for an 84-pack of estradiol and norethisterone tablets, known as hormonal add-back therapy (ABT), is £13.20. At list price, the annual treatment cost per patient is £1,040.00 (without ABT) or £1,097.20 (with ABT).[1]

Relugolix-estradiol-norethisterone acetate

The NHS list price (excluding VAT) of relugolix-estradiol-norethisterone acetate is £72.00 for a 28-pack and £216.00 for an 84-pack. The annual treatment cost per patient is £939.00.[3]

Based on assumptions within the NICE resource impact template for TA996, the estimated cost of implementing this guidance in Cheshire and Merseyside is £166,000 in 2025-26, £169,000 in 2026-27, £171,000 in 2027-28, £174,000 in 2028-29, and £104,000 in 2029-30 when it is assumed that steady state is reached. This is based on drug costs alone.

Effectiveness [1]

Linzagolix is a selective, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist.
The clinical evidence for linzagolix came from 2 randomised controlled trials, PRIMROSE 1 and 2, which compared linzagolix with placebo. The trials were very similar in structure, inclusion and exclusion criteria,

and the outcomes measured. The company explained that because of the similarity of these trials, it was appropriate to give pooled efficacy data up to week 24. The primary outcome for both trials was attainment of response, which was a reduction in HMB defined as menstrual blood loss (MBL) of less than or equal to 80 ml and a greater than or equal to 50% reduction in MBL from baseline. Secondary outcomes included percentage change from baseline in MBL, fibroid volume and uterine volume, pain, percentage change from baseline in haemoglobin in people with anaemia and change in quality of life (uterine fibroids severity and quality of life [UFS-QoL] and EQ-5D-5L instruments). Four different regimens of linzagolix and placebo were compared. The regimens assessed were 100 mg and 200 mg of linzagolix both with and without hormonal ABT. People having any linzagolix dosing regimen were significantly more likely to have a response than placebo. The greatest effect compared with placebo was seen with the 200 mg with hormonal ABT regimen, pooled analysis odds ratio (OR) 10.77 (95% confidence interval [CI] 6.66 to 17.42). The 100 mg without hormonal ABT regimen had the lowest response effect compared with placebo, pooled analysis OR 2.75 (95%CI 1.82 to 4.16), and the remaining regimens, 100 mg plus hormonal ABT and 200 mg without hormonal ABT, had results between these. The committee noted that there appeared to be a placebo effect for the response outcome because 66 people (32%) in the placebo group reported having a reduction in HMB in the pooled PRIMROSE results.

References

1. National Institute for Health and Care Excellence. Technology Appraisal 996; Linzagolix for treating moderate to severe symptoms of uterine fibroids, published 14 August 2024. Accessed 12 September 2024
2. Theramex UK Limited. Summary of product characteristics; Yselty 100mg film coated tablets, 6 August 2024. Accessed 9 August 2024.
3. NHS Business Services Authority. Dictionary of medicines and devices (dm+d) browser. Accessed 03 October 2024.

Patients who are not eligible for treatment under this policy may still be considered for treatment on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. Follow the locally defined process.