Linzagolix or relugolix-estradiol-norethisterone for uterine fibroids

A discussion guide for healthcare professionals and patients

NICE National Institute for Health and Care Excellence

What is this document for?

This discussion guide is provided to support discussions between healthcare professionals and people considering treatment with gonadotropin-releasing hormone (GnRH) antagonists linzagolix or relugolix-estradiol-norethisterone combination therapy (relugolix CT) for uterine fibroids.

Healthcare professionals should refer to the summary of product characteristics (SPC) for full prescribing information (see: linzagolix SPC; relugolix CT SPC). People considering treatment should also see the manufacturer's patient information leaflet (PIL: linzagolix PIL; relugolix CT PIL).

In summary:

- Linzagolix and relugolix CT are licensed, long-term, oral treatment options to manage symptoms of uterine fibroids.
- They reduce menstrual blood loss and pain associated with fibroids, both of which have the potential to improve a person's quality of life.
- Some people experience adverse effects, though not everyone does. These are reported to be mostly mild to moderate in severity and can resolve when estradiol and norethisterone (hormonal add-back therapy) are taken alongside treatment. Relugolix is formulated with add-back therapy included as a combination tablet, whereas with linzagolix this would need to be taken separately.
- Bone mineral density loss has been reported with these medicines and they are not recommended in people at risk of osteoporosis and fractures. Extra monitoring may be needed in people at risk of bone loss.
- Linzagolix and relugolix CT should not be used in pregnancy. Non-hormonal contraception should be used during treatment with linzagolix, and for the first month with relugolix CT. See the NHS summary of non-hormonal contraception for more information.
- The long-term safety of linzagolix and relugolix CT is not yet known.

What does treatment involve?

Linzagolix and relugolix CT are both given as an oral tablet once daily. GnRH antagonists may require concomitant hormonal add-back therapy (ABT) to reduce side effects associated with low levels of oestrogen and progesterone that can result from treatment. Relugolix CT is formulated with hormonal ABT included in the tablet whereas estradiol and norethisterone would need to be taken separately when given with linzagolix, potentially incurring extra prescription charges. Linzagolix can be used long term without hormonal ABT, although a dose reduction is needed following the first 6 months of treatment. This may be preferable in people who cannot, or would prefer not to, have hormonal ABT.

A comparison table of linzagolix (with or without ABT) and relugolix CT is given in Table 1.

Table 1. Prescribing comparison summary of linzagolix with ABT, linzagolix without ABT, and relugolix CT (see: linzagolix SPC; relugolix CT SPC).

	Linzagolix with ABT	Linzagolix without ABT	Relugolix CT
Treatment initiation	Within the first week of the menstrual cycle	Within the first week of the menstrual cycle	Within 5 days of the onset of menstrual bleeding
Recommended dose	Linzagolix 200 mg daily, with estradiol 1 mg and norethisterone 0.5 mg daily	Linzagolix 200 mg daily, reducing to 100 mg daily after 6 months	Relugolix 40 mg, estradiol 1 mg and norethisterone 0.5 mg daily
Tablet burden	2 tablets daily if ABT taken as a combination	1 tablet daily	1 tablet daily
Monitoring requirements	At the start of treatment: • blood pressure • DEXA scan (for people at risk of bone loss) • a negative pregnancy test At 12 months of treatment: • DEXA scan	At the start of treatment: • blood pressure • DEXA scan (for people at risk of bone loss) • a negative pregnancy test At 12 months of treatment: • DEXA scan	At the start of treatment: • blood pressure • DEXA scan (for people at risk of bone loss) • a negative pregnancy test At 12 months of treatment: • DEXA scan
Contraception requirements	At the start of treatment: • any hormonal contraception needs to be stopped During treatment: • non-hormonal methods of contraception must be used	At the start of treatment: • any hormonal contraception needs to be stopped During treatment: • non-hormonal methods of contraception must be used	At the start of treatment: • any hormonal contraception needs to be stopped During treatment: • non-hormonal methods of contraception must be used for at least 1 month after the start of treatment • provides adequate contraception after at least 1 month of use After treatment has stopped: • Alternative contraception needs to be started immediately
Missed doses	Take as soon as possible and then continue the next day at the usual time	Take as soon as possible and then continue the next day at the usual time	If 1 tablet is missed, take as soon as possible and then continue the next day at the usual time If 2 or more tablets are missed for consecutive days, contraceptive protection may be reduced. A non-hormonal method of contraception is to be used for the next 7 days of treatment.

What are the potential benefits?

Linzagolix and relugolix CT are licensed oral treatment options for people with moderate to severe symptoms of uterine fibroids, which can be taken long-term and without the need for subsequent surgery. This contrasts with GnRH agonists (such as leuprorelin and goserelin), which are injections licensed for up to 3 to 6 months only, usually prior to surgery. Sometimes GnRH agonists are used for longer periods, but this is an off-label use.

Linzagolix and relugolix CT do not stimulate hormone release and therefore do not cause the temporary worsening of symptoms (otherwise known as the flare effect) as seen with GnRH agonists.

Menstrual blood loss

Linzagolix and relugolix CT have not been directly compared in clinical trials. However, in their pivotal studies (PRIMROSE 1 and 2 [linzagolix trials; 1012 people] and LIBERTY 1 and 2 [relugolix CT trials; 770 people]) in people with fibroids and heavy menstrual bleeding, reducing menstrual blood loss was the primary endpoint (LIBERTY 1 and 2: Al-Hendy et al. 2021; PRIMROSE 1 and 2: Donnez et al. 2022).

Both linzagolix and relugolix CT were better than placebo at reducing the total volume of menstrual blood loss and at producing amenorrhoea following 24 weeks of treatment (see Table 2 on page 5).

Anaemia

All 4 studies found improvements in haemoglobin levels in people with anaemia by week 24 compared with placebo.

In the PRIMROSE trials, improvements were greater with the higher doses of linzagolix; and the addition of hormonal ABT did not decrease the observed effects. The LIBERTY trials for relugolix CT found that by week 24, 56 in 100 people with anaemia at baseline had an increase of more than 20 g per litre in haemoglobin levels, although 44 in 100 did not see this effect (Al-Hendy et al. 2021, Donnez et al. 2022).

Pain reduction

In all 4 studies people self-reported their pain at baseline, and at week 24 of treatment. All studies found a greater proportion of people reported a reduction in pain with linzagolix or relugolix CT when compared with placebo. Only the PRIMROSE (linzagolix) studies reported this reduction to be clinically significant; the LIBERTY (relugolix CT) studies did not report if this reduction was clinically significant. Pain reduction appeared to be larger when 200 mg of linzagolix was taken, and hormonal ABT did not appear to provide any additional benefit (Al-Hendy et al. 2021, Donnez et al. 2022).

Table 2. Treatment outcomes seen in people with uterine fibroids treated with linzagolix, relugolix CT, or placebo, at week 24 of treatment, on average per 100 people (Al-Hendy, Lukes et al. 2021; Donnez, Taylor et al. 2022).

Area of benefit	**Linzagolix:** 200 mg **Estradiol:** 1 mg **Norethisterone:** 0.5 mg	**Linzagolix:** 200 mg	**Linzagolix:** 100 mg	**Placebo when compared with linzagolix**	**Relugolix CT** (40 mg relugolix + 1 mg estradiol + 0.5 mg norethisterone)	**Placebo when compared with relugolix CT**
Menstrual blood loss of less than 80 mL **and** a 50% or more reduction in menstrual blood loss from baseline	85 saw this / 15 did not	75 saw this / 25 did not	57 saw this / 43 did not	32 saw this / 68 did not	72 saw this / 28 did not	17 saw this / 83 did not
Amenorrhoea	69 saw this / 31 did not	65 saw this / 35 did not	36 saw this / 64 did not	17 saw this / 83 did not	51 saw this / 49 did not	5 saw this / 95 did not

What are the potential harms and unwanted effects?

Side effects

The pivotal studies lasted 24 weeks. In all 4 studies side effects were reported as mild or moderate in severity, with headache and hot flushes most commonly reported. For linzagolix, most reported side effects were dose dependent and seen less frequently with hormonal ABT (see Table 3 on page 7).

The long-term safety of linzagolix and relugolix CT is not yet known.

The increased risk of arterial or venous thromboembolism with medicines containing oestrogen and progesterone must be considered when deciding to prescribe relugolix CT due to its combination formulation.

Linzagolix and relugolix CT are both black triangle medicines. Therefore, all suspected adverse reactions should be reported via the MHRA Yellow Card scheme.

Bone mineral density loss

In all 4 studies bone mineral density (BMD) loss was seen in people who were not co-prescribed hormonal ABT. BMD loss was largely mitigated by hormonal ABT but was still slightly higher than placebo (Al-Hendy et al. 2021, Donnez et al. 2022).

Some people may need a dual-energy X-ray absorptiometry (DEXA) scan before initiating these medicines. See Table 1 on page 3 and the NICE guideline on osteoporosis and assessing the risk of fragility fracture for further information.

Special populations

Linzagolix and relugolix CT must not be used in people with severe hepatic impairment. Linzagolix is contraindicated in people with moderate or severe renal impairment (eGFR less than 60 mL/min), and in people with end-stage renal disease. Relugolix CT has not been studied in people who need haemodialysis. See the SPCs (linzagolix SPC; relugolix CT SPC) for more information on when these medicines should be used with caution.

Further contraindications and cautions may apply when prescribing additional hormonal ABT: see the relevant SPC for more information.

Interactions

Both linzagolix and relugolix CT are partially metabolised by the liver, and this can lead to interactions with other medicines metabolised this way. See the SPCs (linzagolix SPC; relugolix CT SPC) or BNF for drug interactions with linzagolix or relugolix CT.

Table 3. Commonly reported side effects in people with uterine fibroids treated with linzagolix and relugolix CT, at week 24 of treatment, on average per 100 people (Al-Hendy, Lukes et al. 2021; Donnez, Taylor et al. 2022). Details of other potential harms and unwanted effects are given on page 6.

Side effect	**Linzagolix:** 200 mg **Estradiol:** 1 mg **Norethisterone:** 0.5 mg	**Linzagolix:** 200 mg	**Linzagolix:** 100 mg	**Placebo when compared with linzagolix**	**Relugolix CT** (40 mg relugolix + 1 mg estradiol + 0.5 mg norethisterone)	**Placebo when compared with relugolix CT**
	Treatment dose and outcome (on average per 100 people)					
Hot flushes	10 saw this / 90 did not	33 saw this / 67 did not	10 saw this / 90 did not	5 saw this / 95 did not	8 saw this / 92 did not	6 saw this / 94 did not
Headache	8 saw this / 92 did not	12 saw this / 88 did not	6 saw this / 94 did not	6 saw this / 94 did not	10 saw this / 90 did not	13 saw this / 87 did not
Fatigue	< 5 saw this / > 95 did not	< 5 saw this / > 95 did not	< 5 saw this / > 95 did not	< 5 saw this / > 95 did not	2 saw this / 98 did not	3 saw this / 97 did not
Hyperhidrosis or night sweats	0 saw this / 100 did not	3 saw this / 97 did not	1 saw this / 99 did not	< 1 saw this / > 99 did not	≤ 3 saw this / ≥ 97 did not	≤ 3 saw this / ≥ 97 did not
Hypertension	**Not reported**	**Not reported**	**Not reported**	**Not reported**	5 saw this / 95 did not	2 saw this / 98 did not

Safety in pregnancy and contraception

Linzagolix and relugolix CT are not recommended in pregnancy. Both treatments can make occurrence of pregnancy harder to identify in a timely manner; therefore, a pregnancy test should be done if pregnancy is suspected, and treatment discontinued if pregnancy is confirmed.

Linzagolix with or without ABT has not been proven to provide contraceptive cover, but relugolix CT can after 1 month of treatment; see Table 1 on page 3 for more contraception advice.

Alternatives to linzagolix and relugolix CT

Fibroids do not need to be treated if they are not causing symptoms. After the menopause, they will often shrink without treatment.

There are other options for symptom management which may be suitable if linzagolix or relugolix CT are not. Uterine fibroids can also be managed with surgical and non-surgical procedures, such as a hysterectomy, myomectomy, or uterine artery embolisation (see the NICE guideline on heavy menstrual bleeding and the NHS summary of fibroid treatment).

References

- Donnez J, Taylor H, Stewart E, et al. (2022) Linzagolix with and without hormonal add back therapy for the treatment of symptomatic uterine fibroids (PRIMROSE 1 and 2): two randomised, placebo-controlled, phase 3 trials. Lancet 400(10356): 896–907.
- Al-Hendy A, Lukes A, Poindexter A, et al. (2021) Treatment of Uterine Fibroid Symptoms with Relugolix Combination Therapy. New Engl J Med 384(7): 630–42.
- Heavy menstrual bleeding: assessment and management (2018) NICE guideline NG88.
- Linzagolix for treating moderate to severe symptoms of uterine fibroids (2024) NICE technology appraisal guidance 996.
- Relugolix-estradiol-norethisterone acetate for treating moderate to severe symptoms of uterine fibroids (2022) NICE technology appraisal guidance 832.

ISBN: 978-1-4731-9454-0