National Institute for Health and Care Excellence

Health Technology Evaluation

Linzagolix for treating moderate to severe symptoms of uterine fibroids ID6190

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Theramex	We believe that it is important for NICE to evaluate linzagolix as a treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. Based on the clinical evidence, linzagolix provides patients with improvements in endpoints such as reduced menstrual blood loss, uterine fibroid volume reduction, improved Hb levels, and improvements from baseline in mean UF-related pain scores across all treatment arms, both with, and without hormone-based therapy (HBT). Compared to current therapies used for the treatment of UF, linzagolix is well tolerated for long-term use.	Thank you for your comment. As a portion of the population who would have linzagolix does not have a NICE recommended comparator, the cost-comparison process is not suitable for this appraisal.

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		Additionally, as the only GnRH antagonist that can be used without hormone-based therapies, linzagolix serves an unmet need and offers flexibility to meet individual women's needs. In the draft scope, it states, "NICE is considering evaluating this technology through its cost comparison evaluation process". We think linzagolix provides a similar or greater health benefit, at a similar or lower cost, compared with technologies that have previously been recommended in published NICE guidance for this indication. Therefore, we consider it appropriate for linzagolix to be evaluated via the cost-comparison route, as suggested in the draft scope.	
Wording	Theramex	We agree with the stated remit "To appraise the clinical and cost effectiveness of linzagolix within its marketing authorisation for treating uterine fibroids"	Thank you for your comment.
Additional comments on the draft remit	Theramex	No other comments.	N/A

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Theramex	Overall, the background information section is accurate. However, we would like to offer some additional points and slight alterations to provide additional clarity to the background information section. To facilitate its implementation into the final scope, we have pasted the whole section below with deleted text stricken through, and added text highlighted in yellow and referenced throughout. Uterine fibroids (UFs) are noncancerous tumours of the uterus. Fibroids are common, with around two in three women developing at least one UF at some point in their life.(3) ~~The exact cause of fibroids is not known, but they have been linked to the hormone oestrogen.~~[1] The exact aetiology of UFs is unknown, however, they are oestrogen- and progesterone-dependent and as such, develop during a woman's reproductive years (age range 16 to 50 years)(4, 5) Approximately 25% to 30% of women with UFs experience symptoms (6) ~~but they~~ which can cause significant morbidity. Approximately one-third of women with UFs have chronic, heavy menstrual blood loss (HMB), the most common symptom of UFs. Other menstrual bleeding-related symptoms include prolonged menstrual bleeding, spotting	Thank you for your comments. These were considered whilst updating the draft scope to the final scope.

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		between menstrual cycles, frequent menstrual cycles, anaemia, lower back and menstrual pain and cramping(7). In a small proportion of women, complications with fibroids can interfere with pregnancy or cause infertility.[1] The type and severity of symptoms is influenced by the location, size and number of fibroids.[2] Fibroids are generally classified by their location. Intramural fibroids grow within the muscular uterine wall. Submucosal fibroids grow in the muscle layer beneath the uterus's inner lining and grow into the uterine cavity. Subserosal fibroids develop outside of the uterus and grow into the pelvis. The prevalence of symptomatic fibroids is low in women younger than 30 years but is between 20 to 50% in women older than 30 years.[3] Risk factors for uterine fibroids include race, family history of fibroids, age and obesity.[4] Black women have a two–threefold increased risk of UFs. Moreover, Black women are more likely to have multiple and larger fibroids five to six years earlier and have higher rates of hospitalisations and surgical intervention compared with White women(8-10). Oestrogen and progesterone control the proliferation and maintenance of uterine fibroids. Most medical treatments act by interfering with their production or function.[4] For people with uterine fibroids less than 3 cm in diameter and do not cause distortion of the uterine cavity, NICE guideline 88 (NG88) recommends considering a levonorgestrel-releasing intrauterine system (LNG-IUS) for the treatment of heavy menstrual bleeding. If heavy menstrual bleeding worsens	

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		or an LNG-IUS is not suitable, pharmacological treatments (such as tranexamic acid and non-steroidal anti-inflammatory drugs) and hormonal treatments (such as combined hormonal contraception, cyclical oral progestogens and gonadotrophin-releasing hormone analogues) are recommended. Surgery (second-generation endometrial ablation or hysterectomy) is recommended as an option if treatment is unsuccessful or declined, or symptoms are severe. For people with submucosal uterine fibroids less than 3 cm in diameter, hysteroscopic removal should be considered. For people with uterine fibroids of 3 cm or more in diameter, the same pharmacological and surgical treatments are recommended as options as well as uterine artery embolisation and myomectomy. Pre-treatment with a gonadotrophin-releasing hormone analogue before hysterectomy and myomectomy should be considered if uterine fibroids are causing an enlarged or distorted uterus. NICE technology appraisal 832 recommends relugolix-estradiol-norethisterone acetate as an option for treating moderate to severe symptoms of uterine fibroids in adults of reproductive age.	
Population	Theramex	The population as defined in the draft scope needs to be amended to the following to match the licensed indication for Linzagolix: “People with moderate to severe symptoms associated with uterine fibroid(s) of reproductive age”	Thank you for your comment. The final scope has been amended to reflect this.
Subgroups	Theramex	There are no subgroups within the target patient population that should be considered differently.	Thank you for your comment. Subgroups

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			have been added to the final scope to reflect the distinct populations highlighted in the company's response to the comparators section. The committee will consider subgroups where the evidence allows.
Comparators	Theramex	The current treatment pathway in England and Wales for moderate to severe based on NG88 and TA832 shows that non-hormonal treatments such as tranexamic acid and NSAIDS, and hormonal-based treatments such as LNG-IUS, CoCs, and oral progestogens are used as first-line therapies. Linzagolix is being positioned as a second-line therapy for women with moderate to severe symptoms of uterine fibroids for three distinct clinical scenarios. Therefore, the above first-line therapies are not considered relevant comparators for linzagolix. The three clinical scenarios where linzagolix would be used are the following: 1. **Short-term use (≤6 months) before surgery / interventional procedure (with/without hormone-based therapy)** Relevant comparators: GnRH agonists (leuprolide, triptorelin, goserelin), and relugolix,	Thank you for your comment. The final scope has been amended to reflect the most appropriate comparators for this appraisal.

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		2. Long-term use with HBT Relevant comparator: Relugolix **3. Long-term use without HBT** No relevant therapeutic comparators	
Outcomes	Theramex	Yes, they are in line with the outcomes measured in both the PRIMROSE 1 & 2 Phase III clinical trials.	Thank you for your comment.
Equality	Theramex	We do not believe the current remit or scope could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which linzagolix is licensed. We do not believe the draft remit and scope could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population. We do not believe the draft remit and scope could have any adverse impact on people with a particular disability or disabilities. Additionally, we believe that recommending linzagolix would adequately address equality concerns that were highlighted in the relugolix NICE TA832. We believe linzagolix will: 1. Provide a therapy that is available to everyone with uterine fibroids who are eligible. This may include people who are trans or non-binary.	Thank you for your comments. The committee will consider all potential equalities issues during the course of the appraisal.

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		2. Provide an effective pharmacological treatment for everyone who, due to historic or cultural beliefs, cannot or does not wish to take HBT. 3. Provide a broader treatment option, with increased dosing flexibility, for communities that have historically seen inequalities for access to specialist care, particularly within the Black community. Reduce costs for people from lower socioeconomic groups. It was highlighted in the NICE FAD for relugolix that 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 and may increase the 'did not attend' rate at clinics.	
Other considerations	Theramex	N/A	N/A
Questions for consultation	Theramex	N/A	N/A
Additional comments on the draft scope	Theramex	N/A	N/A

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope