NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Relugolix with oestradiol and norethindrone acetate for heavy menstrual bleeding associated with uterine fibroids

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of relugolix with oestradiol and norethindrone acetate within its marketing authorisation for treating heavy menstrual bleeding associated with uterine fibroids.

Background

Uterine fibroids are noncancerous growths of the uterus. Most are asymptomatic, but they can cause significant morbidity including prolonged or heavy menstrual bleeding, pelvic pressure or pain and contribute to infertility or problems during pregnancy. The type and severity of symptoms is influenced by the location, size and number of fibroids.[1] 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 most common symptom of uterine fibroids is heavier than normal or prolonged menstrual bleeding.[2] Heavy menstrual bleeding is defined as excessive menstrual blood loss which interferes with physical, social and emotional quality of life.

Heavy menstrual bleeding is common, affecting 20 to 30% of women of reproductive age.[3] Fibroids usually develop during the reproductive years (from around 16 to 50 years) when oestrogen levels are at their highest.[2] 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.[4] Risk factors for uterine fibroids include race, family history of fibroids, age and obesity.[5]

Oestrogen and progesterone control the proliferation and maintenance of uterine fibroids. Most medical treatments act by interfering with their production or function.[5]

For people with uterine fibroids less than 3 cm in diameter and not causing 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 or an LNG-IUS is not suitable, pharmacological and hormonal treatments are recommended, including tranexamic acid, non-steroidal anti-inflammatory drugs, combined hormonal contraception or cyclical oral progestogens. 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.

The technology

Relugolix (Relumina, Gedeon Richter) is a small molecule that binds to the gonadotrophin-releasing hormone receptor in the pituitary gland, decreasing the downstream production of oestrogen and progesterone by the ovaries. It is administered orally.

Relugolix does not currently have a marketing authorisation in the UK for treatment of heavy menstrual bleeding associated with uterine fibroids. It has been studied in clinical trials in combination with oestradiol and norethindrone acetate compared with placebo in premenopausal women aged 18 to 50 years old with heavy menstrual bleeding associated with uterine fibroids.

Intervention(s)	Relugolix with oestradiol and norethindrone acetate
Population(s)	People with heavy menstrual bleeding associated with uterine fibroids
Comparators	Established clinical management without relugolix with oestradiol and norethindrone, including: • levonorgestrel-releasing intrauterine system (LNG-IUS; off-label for some LNG-IUSs) • tranexamic acid • non-steroidal anti-inflammatory drugs (off-label) • combined hormonal contraception (off-label for some combined hormonal contraceptives) • cyclical oral progestogens • gonadotrophin-releasing hormone analogues
Outcomes	The outcome measures to be considered include: • change in menstrual blood loss volume • time to menstrual blood loss response • pain • rates of bladder infections • haemoglobin levels • hormone levels • mortality • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.
Other considerations	If the evidence allows the following subgroups will be considered: • people with fibroids less than 3 cm in diameter • people with fibroids of 3 cm or more in diameter Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals**: Fluid-filled thermal balloon and microwave endometrial ablation techniques for heavy menstrual bleeding (2004). NICE Technology Appraisal 78. Guidance on the static list. **Related Guidelines**: Heavy menstrual bleeding: assessment and management (2018). NICE guideline NG88. Review date to be confirmed. **Related Interventional Procedures:** Ultrasound-guided high-intensity transcutaneous focused ultrasound for symptomatic uterine fibroids (2019). NICE interventional procedures guidance 657. Hysteroscopic morcellation of uterine leiomyomas (fibroids) (2015). NICE interventional procedures guidance 522. Magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids (2011). NICE interventional procedures guidance 413. Uterine artery embolisation for fibroids (2010). NICE interventional procedures guidance 367. Magnetic resonance (MR) image-guided percutaneous laser ablation of uterine fibroids (2003). NICE interventional procedures guidance 30.

	Laparoscopic laser myomectomy (2003). NICE interventional procedures guidance 23. **Interventional Procedures in development**: Transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids. Publication expected March 2021. Laparoscopic morcellation of uterine fibroids. Publication date to be confirmed. Hysteroscopic morcellation of uterine leiomyomas (fibroids). Publication date to be confirmed. **Related Quality Standards**: Heavy menstrual bleeding (2018). NICE quality standard 47. **Related NICE Pathways**: Heavy menstrual bleeding (2020). NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 2, 4 and 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Will relugolix with oestradiol and norethindrone acetate be used as an addition to current standard care, or would it replace current standard care options?

Are surgical (hysterectomy and myomectomy) and non-surgical procedures (second-generation endometrial ablation, hysteroscopic removal and uterine artery embolisation) relevant as comparators for relugolix with oestradiol and norethindrone acetate?

Have all relevant comparators for relugolix with oestradiol and norethindrone acetate been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for heavy menstrual bleeding associated with uterine fibroids?

Are the outcomes listed appropriate?

Are symptoms of uterine fibroids other than heavy menstrual bleeding expected to improve with relugolix with oestradiol and norethindrone acetate? If yes, which?

Are there any subgroups of people in whom relugolix with oestradiol and norethindrone acetate is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider relugolix with oestradiol and norethindrone acetate will fit into the existing NICE pathway: heavy menstrual bleeding?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which relugolix will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider relugolix with oestradiol and norethindrone acetate to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of relugolix with oestradiol and norethindrone acetate can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1. Mayo Clinic. Uterine fibroids: symptoms and causes. Accessed November 2020.

2. NHS. Fibroids. Accessed November 2020.

3. Royal College of Obstetricians and Gynaecologists. National Heavy Menstrual Bleeding Audit. May 2011

4. BMJ Best Practice: uterine fibroids. Accessed November 2020.

5. Lumsden M.A.; Fibroids: diagnosis and management; BMJ; 351:h4887; 2015