NICE National Institute for Health and Care Excellence

2021 exceptional surveillance of heavy menstrual bleeding: assessment and management (NICE guideline NG88)

Surveillance report

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Surveillance decision

We will reinstate ulipristal acetate 5 mg (Esmya) as an option for the treatment of uterine fibroids greater than 3 cm diameter in recommendation 1.5.10. We will reinstate recommendations about when to offer ulipristal acetate, the risk associated with its use and course of treatment that currently comprise withdrawn recommendations 1.5.11 and 1.5.12. We will amend these recommendations to highlight ulipristal acetate's restricted indication, emphasise the risk of liver injury associated with its use and the measures that should be put in place to mitigate this risk.

We will not reinstate recommendation 1.5.17 about the use of ulipristal acetate as a presurgical treatment at this time as this is now an off-label use. We will flag presurgical management of uterine fibroids as an area for which to look for evidence at the next surveillance review.

The reasons for the decision

The NICE guideline on heavy menstrual bleeding recommended ulipristal acetate for women with fibroids of 3 cm or more in diameter. But following reports of severe liver injury resulting in liver transplant in 5 women receiving ulipristal acetate, the MHRA suspended the licence in March 2020 and the relevant NICE guideline recommendations were temporarily withdrawn. The MHRA reinstated the licence in February 2021 but restricted indications to only intermittent treatment of moderate to severe symptoms of uterine fibroids before menopause and when surgical procedures (including uterine fibroid embolisation) are not suitable or have failed.

We consulted with topic experts from the NICE expert advisers database with expertise in gynaecology about the proposals. We specifically asked if withdrawing ulipristal acetate as presurgical treatment would cause issues in practice. Four experts including 2 of the original committee members responded to say they agreed with the proposals to edit the recommendations and that withdrawing ulipristal acetate as a presurgical option would not impact practice.

Methods

The exceptional surveillance process consisted of:

- Examining the MHRA drug safety update that triggered the exceptional review alongside the evidence used to develop the ulipristal acetate recommendations in 2016.
- Feedback from a NICE clinical adviser.
- Consulting with guideline committee members and topic experts with expertise in gynaecology.
- Further literature searches were not needed as the available information was sufficient for decision making.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Consultation with committee members and topic experts

We consulted on these proposals with 5 topic experts with expertise in gynaecology including 2 members of the original committee for this NICE guideline. Five experts responded. Four experts including 2 committee members responded to say they agreed with the proposals, the fifth felt this was outside of their area of expertise and did not comment. One expert who responded advised it is important to include in any reinstatement wording that emphasises the central role of patient choice and informed consent about treatments for uterine fibroids. They advised reinstating wording in recommendation 1.5.12 which recommended ulipristal acetate for 'women who are not eligible for surgery for example where the risks of surgery outweigh the benefits or where the woman declines surgical treatment.' We will reinstate this wording and also wording from recommendation 1.5.11 which recommends to 'advise women of the signs and symptoms of liver injury' in line with the latest MHRA advice.

A further expert responded that in their local setting ulipristal acetate was not being used prior to surgical treatment and gonadotrophin-releasing hormone analogues are being prescribed as the drug of choice. This intelligence is consistent with recommendation 1.5.17.

History of the guideline

The NICE guideline for heavy menstrual bleeding was first published in 2007 (NICE guideline CG44). Ulipristal acetate 5 mg was first authorised in 2012 for intermittent or preoperative treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age. In 2018, the original guideline was updated and replaced by NICE guideline NG88 which included recommendations about ulipristal acetate.

Development of the 2018 recommendations

The recommendations for ulipristal acetate were based on the results of 3 randomised controlled trials that investigated effectiveness in women of reproductive age with symptomatic fibroids of at least 3 cm diameter. An economic model constructed for the guideline found ulipristal acetate to be well within the bounds of NICE's cost effectiveness threshold compared to no treatment.

The committee agreed that it was important to have separate recommendations to reflect the strong evidence base covering women with anaemia and drafted recommendations stratified by haemoglobin level. The committee agreed that there was no difference in effectiveness between ulipristal acetate 5 mg or 10 mg. The committee agreed to recommend 5 mg ulipristal acetate for up to 4 courses based on efficacy and safety data from the included studies. These recommendations were consistent with the marketing authorisation.

MHRA safety review 2018

Before recommendations from this rapid update could be published an MHRA safety alert was published in August 2018. This review was initiated by 4 cases of severe liver injury resulting in liver transplantation in women receiving ulipristal acetate. As a result, the MHRA restricted ulipristal acetate's indication to no more than 1 treatment course in women who are not eligible for surgery, and liver function monitoring to be carried out in all women treated with ulipristal acetate. NICE temporarily withdrew its recommendations about ulipristal acetate and republished amended recommendations to take account of restrictions to the indication and the requirement to monitor liver function. The amended recommendations advised ulipristal acetate for 1 course (lasting up to 3 months) of preoperative treatment for moderate to severe symptoms of uterine fibroids and for intermittent treatment of moderate to severe symptoms of uterine fibroids. The guideline also recommended advising women of the signs and symptoms of liver injury and

monitoring liver function for the first 2 treatment courses. In women who are not eligible for surgery it recommended offering 5 mg doses (up to 4 courses) to those women with anaemia and to consider offering it to women without anaemia.

MHRA safety review 2020

In March 2020, the MHRA temporarily suspended marketing authorisations for all ulipristal acetate 5 mg products following a fifth case of liver injury requiring transplant in women receiving it. This occurred despite monitoring of liver function advised by the 2018 safety review.

In response NICE guideline recommendations about ulipristal acetate were temporarily withdrawn for a second time in March 2020 pending publication of the MHRA safety review, as described on the guideline update information page.

MHRA safety review 2021

The latest MHRA safety update from February 2021 advises that the MHRA has reinstated ulipristal acetate's licence but with restricted indications. The review concluded that the benefits of ulipristal acetate 5 mg in controlling fibroids may outweigh the risk of liver injury in women who have no other treatment options. Ulipristal acetate 5 mg should only be used for intermittent treatment of moderate to severe symptoms of uterine fibroids before menopause and when surgical procedures (including uterine fibroid embolisation) are not suitable or have failed.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

After considering the MHRA safety review and consulting with topic experts, we will reinstate recommendations about ulipristal acetate for the treatment of uterine fibroids greater than 3 cm diameter. Editorial amendments will be made that highlight its restricted marketing authorisation and associated risk.

At this time, we will not reinstate the recommendation about presurgical use of ulipristal

acetate.

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