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Esmya: new measures to minimise risk of rare but serious liver injury

EMA concludes review of medicine for uterine fibroids

The European Medicines Agency (EMA) has recommended that several measures be put in place to minimise the risk of rare but serious liver injury with Esmya (ulipristal acetate). Certain women may start treatment with Esmya once the new measures are implemented.

The measures include: contraindication in women with known liver problems; liver tests before, during and after stopping treatment; a card for patients to inform them about the need for liver monitoring and to contact their doctor should they develop symptoms of liver injury. In addition, use of the medicine for more than one treatment course has been restricted to women who are not eligible for surgery.

Esmya is used to treat moderate to severe symptoms of uterine fibroids (benign tumours of the womb). The medicine has been shown to be effective at reducing bleeding and anaemia associated with the condition, as well as the size of the fibroids.

The review of Esmya was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) following reports of serious liver injury, including liver failure leading to transplantation. The PRAC concluded that Esmya may have contributed to the development of some cases of serious liver injury.[1]

The PRAC therefore recommended that use of the medicine should be restricted. It also recommended that studies should be performed to determine the effects of Esmya on the liver and whether the new measures are effective in minimising the risks.

The PRAC's recommendations have now been endorsed by EMA's Committee for Medicinal Products for Human Use (CHMP) and will be sent to the European Commission for a final legal decision. A letter will be sent to doctors to inform them of the new conditions of use, which will become applicable after a Commission decision is issued.

[1] In 8 cases of serious liver injury, a role of Esmya in contributing to these cases is possible. It is estimated that around 765,000 patients have been treated with Esmya to date.

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Information for patients

- The medicine Esmya, used to treat uterine fibroids, has been reviewed because cases of serious liver problems have occurred in women taking the medicine, including four cases that resulted in liver transplantation.
- Esmya will not be prescribed to you if you have liver problems.
- A liver test will be performed before you start treatment and if the test is abnormal, treatment with Esmya will not be started.
- You will also have liver tests during treatment and after treatment has stopped.
- If no liver problems are detected, a single course of Esmya can be used in women who are about to have surgery for their fibroids; Esmya can be used for more than one course only in women who cannot have surgery.
- A card will be included in the package of the medicine with information on the risk of liver injury and the need for liver monitoring.
- You should stop treatment and contact your doctor immediately if you develop symptoms of liver injury (such as tiredness, yellowing of the skin, darkening of the urine, nausea and vomiting).
- If you have any questions or concern about your treatment, speak to your doctor or pharmacist.

Information for healthcare professionals

- Four cases of serious liver injury leading to hepatic transplantation and additional cases of hepatic injury have been reported in patients treated with Esmya (ulipristal acetate). Although uncertainties around causality remain, the following measures to minimise a possible risk for liver injury will be introduced:
  - Contraindication in patients with underlying liver disorders.
  - Restricted indication in the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age: Esmya should only be used in women who are not eligible for surgical treatment. (Esmya continues to be indicated for one course (lasting up to 3 months) of pre-operative treatment for moderate to severe symptoms of uterine fibroids in adult women of reproductive age.)
  - Liver function tests to be performed before starting each treatment course, monthly during the first 2 treatment courses, and thereafter as clinically indicated. Liver testing also to be performed again 2-4 weeks after stopping treatment.
  - Esmya should not be started if levels of alanine transaminase (ALT) or aspartate aminotransferase (AST) are more than 2 times the upper limit of normal (ULN).
  - Treatment should be stopped in patients with ALT or AST levels more than 3 times ULN.
- Healthcare professionals should advise their patients about the signs and symptoms of liver injury and the action to take should they occur. In case of signs or symptoms suggestive of such injury, treatment should be stopped. Patients should be investigated immediately including liver function testing.
- Healthcare professionals prescribing Esmya in the EU will receive a letter with further details once a European Commission decision has been issued.

More about the medicine

Esmya was authorised in the EU in 2012 for the treatment of moderate to severe symptoms of uterine fibroids, which are benign (non-cancerous) tumours of the womb, in women who have not reached the menopause.

The active substance in Esmya, ulipristal acetate, works by attaching to the targets on cells (receptors) that the hormone progesterone normally attaches to, preventing progesterone from having its effect. Since progesterone may promote the growth of fibroids, by preventing the effects of progesterone ulipristal acetate reduces the size of the fibroids.

More information on Esmya can be found here.

Ulipristal acetate is also the active substance of a single-dose medicine authorised for emergency contraception, ellaOne. No cases of serious liver injury have been reported with ellaOne and there are no concerns with this medicine at this time.

More about the procedure

The review of Esmya was initiated at the request of European Commission on 30 November 2017, under Article 20 of Regulation (EC) No 726/2004.

The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines.

While the review was ongoing, the PRAC had issued temporary recommendations that no new patients should start treatment.

The PRAC issued its final recommendations on 17 May 2018, replacing the temporary measures. The PRAC's final recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted an opinion.

The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States in due course.