臺北醫學大學附設醫院
TAIPEI MEDICAL UNIVERSITY HOSPITAL

藥物不良反應工作小組藥物安全警訊通告 107.06

歐洲藥物管理局(EMA)用藥安全資訊風險溝通：

降低Esmya® (Ulipristal acetate)引起罕見的嚴重肝臟損傷之建議

摘要說明：

2018 年 2 月 EMA 發佈有關 Esmya® (Ulipristal acetate)引起嚴重肝功能損傷的罕見案例之風險，交由藥物安全監視風險評估委員會(PRAC)執行後續評估並提出建議。於 2018/5/18 及 6/1 發佈相關建議。

目前預估已有約 765,000 病患使用過 Esmya® 治療，已確定有 8 件與 Esmya® 相關的嚴重肝功能損傷案件，其中四件案例需接受肝臟移植治療。

醫療人員注意事項：

1) 有肝臟功能問題的婦女不應使用 Esmya® 。
2) 開始使用 Esmya® 前應監測肝臟功能，若肝臟酵素值大於正常值的兩倍，則不應使用 Esmya® 。
3) 在療程期間應每月監測一次肝臟功能，並於結束療程後二~四周內再次監測。若檢查結果大於正常值的三倍以上，應停止服用 Esmya® 並密切觀察病人情況。
4) 已完成一輪 Esmya® 療程的病人，若欲再次執行相同的療程或延長療程，請謹慎評估並應定期監測肝臟功能指數。需要一個以上療程的病患條件應為不合手術條件的婦女。
5) 醫療人員應提醒病人若出現噁心、嘔吐、眼睛或皮膚變黃、感到虛弱、上腹疼痛及食慾不振等症狀應立即就醫或諮詢醫療人員，並應檢測肝臟功能。
6) 醫療人員若懷疑病人因為使用藥品導致不良反應發生時，請立即線上通報藥物不良反應及登入於藥物過敏/不良反應記錄中。

院內品項：
Esmya® (Ulipristal acetate) 5 mg/tab 恩惜膜錠劑

北醫藥物不良反應工作小組 敬啟
臨床藥學組 呂懷恩 藥師
(分機 8443/8444)

1 June 2018
EMA/355940/2018

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.

18 May 2018
EMA/289137/2018

PRAC recommends new measures to minimise risk of rare but serious liver injury with Esmya for fibroids

Regular liver function testing required during treatment

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed its review of Esmya (ulipristal acetate), following reports of serious liver injury. After considering all the evidence, the PRAC concluded that the medicine must not be used in women with liver problems and that certain other patients may start new treatment courses provided they have regular liver tests.

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, as well as the size of the fibroids.

The PRAC has concluded that Esmya may have contributed to the development of some cases of serious liver injury.[1] The Committee has therefore made the following recommendations to minimise this risk:

- Esmya must not be used in women with known liver problems.
- A liver function test should be performed before starting each treatment course and treatment must not be started if liver enzyme levels are more than 2 times the upper limit of normal.
- Liver function tests should be performed once a month during the first two treatment courses and two to four weeks after stopping treatment. If the test is abnormal (liver enzyme levels more than 3 times the upper limit of normal), the doctor should stop treatment and closely monitor the patient.
- Esmya should be used for more than one treatment course only in women who are not eligible for surgery. Women who are about to have surgery should continue to use only one course.
- A card will be included in the box of the medicine to inform patients about the need for liver monitoring, and to contact their doctor should they develop symptoms of liver injury (such as tiredness, yellowing of the skin, darkening of the urine, nausea and vomiting).
- Studies should be performed to determine the effects of Esmya on the liver and whether these measures are effectively minimising the risks.

[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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In February 2018, while the review was ongoing, the PRAC had issued temporary recommendations that no new patients should be started on Esmya. Having finalised its review, the Committee has now concluded that new patients can start treatment in line with the above recommendations to minimise the risk of liver injury.

The PRAC's recommendations will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP) for the adoption of EMA's final opinion, and this will then go to the European Commission for a final legal decision. A letter will be sent to doctors to inform them of the new restrictions of use, which will become applicable after a Commission decision is 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.

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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 has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations.

On 8 February 2018, while the review was ongoing, the PRAC issued temporary recommendations.

The PRAC's final recommendations will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt an opinion.

The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States. The new restrictions on the use of Esmya will become applicable after a Commission decision is issued.