

Drug Safety Update



MHRA

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.



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First, we remind you of new measures to minimise risk of serious liver injury in women receiving Esmya for the symptoms uterine fibroids (page 2). See article on page 2 for new restrictions to use and requirements for liver function monitoring in all women before, during, and after treatment. Use of more than one treatment course is now limited to women who are not eligible for surgery.

Next, this month see page 5 for a list of drug alerts and recalls issued by MHRA in July 2018. These alerts will join the regular monthly sections that highlight and remind you of recent communications about the safety of medicines and medical devices. Remember to check these sections every month for news on the safety of medicines or medical devices used in the care of your patients.

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Esmya (ulipristal acetate) and risk of serious liver injury: new restrictions to use and requirements for liver function monitoring before, during, and after treatment

More than one treatment course is authorised only in women who are not eligible for surgery, and liver function monitoring is to be carried out in all women treated with Esmya. Before initiation, discuss with women the rare risk of liver damage and advise them to seek urgent medical attention if they develop any symptoms or signs of liver injury.

Advice for healthcare professionals:

Restricted indication and new contraindication

- Esmya is now indicated for:
 - the intermittent treatment¹ of moderate to severe symptoms of uterine fibroids in women of reproductive age who are not eligible for surgery
 - one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age
- Esmya treatment is to be initiated and supervised by physicians experienced in the diagnosis and treatment of uterine fibroids
- Esmya is contraindicated in women with underlying liver disorders

Liver function monitoring

- before initiation of each treatment course: perform liver function tests; do not initiate Esmya in women with baseline alanine transaminase (ALT) or aspartate aminotransferase (AST) more than 2-times the upper limit of normal [ULN]
- during the first 2 treatment courses: perform liver function tests every month
- for further treatment courses: perform liver function tests once before each new course and when clinically indicated
- at the end of each treatment course: perform liver function tests after 2–4 weeks
- stop Esmya treatment and closely monitor women with ALT or AST more than 3-times ULN; consider the need for specialist hepatology referral

Discuss the risk of liver damage with Esmya with women and report any suspected adverse drug reactions

- before initiation of Esmya, discuss with women the rare risk of liver damage and need for liver function testing before, during, and after each treatment course
- advise women to seek urgent medical attention if they develop any symptoms or signs of liver injury (such as tiredness, yellowing of the skin, darkening of the urine, nausea and vomiting)
- pharmacists should provide the new patient card to women when dispensing Esmya; copies of this card are included in the letter sent to healthcare professionals and are available [online](#)
- report any suspected adverse drug reactions to Esmya on a [Yellow Card](#) without delay

¹ Each treatment course should not exceed 3 months and should only be repeated after a break in treatment. See [Summary of Product Characteristics](#) for method of administration.

EU review of risk of serious liver injury

In March 2018, we announced [temporary safety measures](#), including no new patients to be prescribed Esmya, while an EU review investigated the link between Esmya and cases of serious liver injury, including cases requiring liver transplantation.

The EU review concluded that Esmya may have contributed to the development of some of the 8 cases of serious liver injury reported for this drug. It is estimated that around 765,000 patients have been treated with Esmya worldwide to date.

The review recommended restricting the indicated population for Esmya for safety reasons and introduced measures to minimise risk of liver injury. In particular, more than one treatment course is now authorised only in women who are not eligible for surgery, and liver function monitoring is to be carried out in all women treated with Esmya.

Alert issued to healthcare professionals

On 7 August 2018, [an alert was issued to UK healthcare professionals](#) to inform them of the new measures to minimise the risk of serious liver damage. The licence holder also sent a letter by post to specialists, GPs, and pharmacists to inform them of the new advice. These restrictions replace the temporary safety measures introduced in February 2018.

Physicians should carefully consider if Esmya is an appropriate option for their patient, in view of the restricted indication, the new contraindication, and the liver monitoring to be undertaken as described in the letter and the updated [Summary of Product Characteristics](#) for Esmya.

In the UK, as of 13 July, we have received 1 Yellow Card report each of acute hepatitis, hepatic fibrosis, and non-alcoholic fatty liver and 8 reports of abnormal liver function tests in association with Esmya.² Approximately 19,860 treatment courses of Esmya were dispensed in the UK between 1 April 2017 and 31 March 2018.³

Resources available to support safe use

A [Patient Card](#) will be introduced in the medicine's package to remind women of the need to stop treatment and contact their doctor immediately should they develop signs or symptoms of liver injury. The Card also contains a table to help women track their blood tests. Pharmacists should advise women to read the information carefully.

Copies of the card have been included in [the letter to healthcare professionals](#) sent on 1 August 2018 and are available [online](#). For additional hard copies, contact Gedeon Richter (UK) Medical Information at 0207 604 8806 or medinfo.uk@gedeonrichter.eu. This will only be required until packs with the pre-inserted Patient Card reach the market.

The [physician's guide](#) and [pathologist's guide](#) for Esmya have also been updated.

² Reporters are asked to submit Yellow Card reports even if they only have a suspicion that the medicine may have caused the adverse drug reaction. The existence of an adverse drug reaction report does not necessarily mean that the medicine has caused the reaction.

³ Data derived from IQVIA MIDAS 04/2017-03/2018 by MHRA, July 2018. The usage estimate is based on the assumption that each treatment course was of 3 months' duration. The number of courses each woman takes may vary between 1 and 4 courses. The number of courses quoted is a broad estimation and is not therefore equivalent to the number of women who used Esmya.

ellaOne

The emergency contraceptive ellaOne also contains ulipristal acetate in a single dose of 30 mg. No cases of serious liver injury have been reported with ellaOne since it was authorised in the EU in 2009 and there are no concerns or changes to its use at this time.

Report suspected adverse drug reactions on a Yellow Card

The Yellow Card Scheme is vital in helping the Medicines and Healthcare products Regulatory Agency (MHRA) to monitor the safety of all healthcare products in the UK to ensure they are acceptably safe for patients and users. Please report any suspected adverse drug reactions to Esmya without delay, via the [Yellow Card Scheme](#).

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Letters and drug alerts sent to healthcare professionals in July 2018

In July 2018, the following letters were sent from licence holders to healthcare professionals about the safety of medicines:

- Valproate (Epilim ▼, Depakote ▼): new restrictions on use; [pregnancy prevention programme to be put in place](#) (for specialists and specialist nurses managing patients treated with valproate medicines and general practitioners who provide primary care to these patients)
- Valproate (Epilim ▼, Depakote ▼): new restrictions on use: pregnancy prevention programme; [important actions for pharmacists](#)
- Tecentriq ▼ (atezolizumab): [Restriction of indication for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy](#)
- Spinraza ▼ (nusinersen): [reports of communicating hydrocephalus not related to meningitis or bleeding](#)

In July 2018, MHRA issued the following [alerts and recalls for drugs](#):

- [Class 1 Medicines Recall: Action Now – including out of hours Pharmacy Level Recall](#)
5 July 2018– Pharmacies in the UK are being advised to recall all batches of valsartan containing medicines made by Actavis Group PTC (now Accord) and Dexcel Pharma Ltd due to contamination.
- [Class 2 Medicines Recall: Fiasp FlexTouch 100 units/mL solution for injection pre-filled pen manufactured by Novo Nordisk \(MDR 065-06/18\)](#)
9 July 2018 – Novo Nordisk is recalling one batch as a precautionary measure due to the presence of particles in a small number of samples.
- [Melatonin 10mg capsules: Company-led recall](#)
17 July 2018 – IPS Specials are recalling specific batches of Melatonin 10 mg capsules because they have been assigned an incorrect extended expiry date.
- [Class 3 Medicines Recall: Sodium Cromoglicate eye drops and Murine Hayfever Relief eye drops \(MDR 072-05/17\)](#)
30 July 2018 – FDC International Ltd are recalling specific batches of Sodium Cromoglicate 2% w/v Eye Drops 13.5ml and Murine Hayfever Relief 2% w/v Eye Drops 10ml due to the presence of a precipitate, which has been identified as Sodium Cromoglicate, in some bottles.

Please continue to submit your thoughts on how we can improve the communication of medicines safety issues to support safe and effective use through our [10-minute survey](#).

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Medical Device Alerts issued in July 2018

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see [Alerts and recalls for drugs and medical devices](#).

The following alerts were recently issued:

- [Novaline haemodialysis bloodlines used with Baxter/Gambro haemodialysis machines – Recall of specific products due to various problems encountered during clinical use \(MDA/2018/025R\)](#)
12 July 2018 – Manufactured by Vital Healthcare Sdn for distribution by Baxter Healthcare Ltd – specific product codes manufactured in 2017 have functional and assembly issues which may lead to air entering the system, blood loss, clotting and delays in treatment.
- [All Alaris™ and Asena™ GS, GH, CC, TIVA, PK, enteral syringe pumps – risk of uncontrolled bolus of medicine \(MDA/2018/024R\)](#)
12 July 2018 – Manufactured by CareFusion, now Becton Dickinson (BD) Medical – identify and replace the back-plate in the plunger assembly and note updated preventative maintenance schedule for these pumps.

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