

Drug Safety Update



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.



MHRA is accredited by NICE to provide Drug Safety Update. Further information can be found on the NICE Evidence Search portal: www.evidence.nhs.uk/

First, read recommendations from the European Medicines Agency about the immediate suspension of the marketing authorisation and recall of daclizumab (Zinbryta ▼) following reports of serious inflammatory brain disorders, including encephalitis and meningoencephalitis, in patients with multiple sclerosis (page 2).

Second, we tell you of temporary safety measures for Esmya for uterine fibroids while an EU review investigates reports of serious liver injury. While the review conclusions are pending, do not initiate any women to courses of Esmya and regularly monitor liver function in all women who are or have recently taken courses of Esmya. See article on page 3 for monitoring advice, including the need to stop treatment and monitor or refer women if transaminase levels are more than 2-times the upper limit of normal.

Next, note the risk of serious harm with various head lice eradication products if treated hair is exposed to sources of ignition, such as when lighting cigarettes (page 5). Pharmacists should advise parents, caregivers, and the person with head lice, if appropriate, that they should not smoke around treated hair and that it should be kept away from open flames or other sources of ignition, including after overnight application until hair is washed.

Finally, we bring news of how GPs can receive confidential tailored prescribing and quality improvement reports on key topics to support practice-level review of patient safety and individual care plans (page 6). The reports, developed by the Royal College of General Practitioners (RCGP) in conjunction with the Clinical Practice Research Datalink (CPRD), are available for free for GP practices contributing to CPRD. CPRD is a Centre of the MHRA and jointly supported by the National Institute for Health Research (NIHR) that provides access to anonymised UK health data for public health research.

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Daclizumab (Zinbryta ▼): suspension and recall for safety reasons; review patients as soon as possible and start alternative therapy

The European Medicines Agency (EMA) has recommended the immediate suspension of the marketing authorisation and recall of daclizumab (Zinbryta) in the EU following reports of serious inflammatory brain disorders, including encephalitis and meningoencephalitis, in patients with multiple sclerosis.

Advice for healthcare professionals:

- Following the initiation of an urgent safety review, the European Medicines Agency (EMA) recommend that:
 - patients should not be started on daclizumab
 - doctors should contact all patients receiving daclizumab as soon as possible and stop their treatment. Alternative therapy should be considered in line with national recommendations (eg, NICE guidance)
 - doctors should monitor all patients stopping daclizumab for adverse reactions and check their liver function tests at least monthly and more frequently if clinically indicated for up to 6 months after the last dose
 - doctors should advise patients to seek urgent medical attention if they develop severe headache or any symptoms of liver injury such as prolonged fever, abdominal pain, jaundice, dark urine, or unexplained nausea or vomiting; serious immune-mediated hepatic injury can occur up to 6 months after the final dose.
 - patients should talk to their doctor if they have any questions about daclizumab
- The EMA's recommendation to suspend Zinbryta and recall the product is being sent to the European Commission for a legally binding decision

[Announcement from the European Medicines Agency](#), 7 March 2018.

Cases of serious inflammatory brain disorders

An urgent EU-wide review of the safety of daclizumab has started. As of 7 March 2018, the EMA had received reports of 12 patients worldwide who developed serious inflammatory brain disorders, including encephalitis and meningoencephalitis, in association with daclizumab. There have been some fatal cases and most other patients remain critically unwell.

Risk factors have not been identified and most patients did not respond to treatment including corticosteroids and/or plasmapheresis. Available evidence also indicates that daclizumab could be linked to other immune-mediated disorders, such as blood dyscrasias, thyroiditis, or glomerulonephritis.

Worldwide, more than 8,000 patients have been treated with daclizumab in clinical trials and post-marketing. There have been no reported cases of serious inflammatory brain disorders in the UK, in which use of daclizumab has been very low (less than 100 patients) and mainly been in clinical trials. The MHRA have sent letters to the Association of British Neurologists and to patient groups to inform them of the recommendations

The company has also informed EMA of its decision to stop ongoing clinical studies with Zinbryta in the EU. Patients in clinical studies who have any questions should contact the doctor treating them in their study.

Background

[Daclizumab](#) (Zinbryta ▼) 150 mg solution for injection was authorised in the EU in July 2016 for the treatment of adults with relapsing forms of multiple sclerosis. Following a 2017 [review](#) of the medicine's effects on the liver, the use of the medicine was restricted to patients who have tried at least two other disease-modifying treatments and cannot be treated with any other multiple sclerosis treatments. The 2017 review also recommended that liver function should be closely monitored before each daclizumab dose (or more frequently if clinically indicated) and for up to 6 months after the last dose, see [Drug Safety Update, January 2018](#).

Call for reporting

Healthcare professionals should continue to report any suspected adverse drug reactions to daclizumab to the [Yellow Card Scheme](#).

Article citation: Drug Safety Update volume 11 issue 8; March 2018: 1.

Esmya (ulipristal acetate) for uterine fibroids: do not initiate or re-start treatment; monitor liver function in current and recent users

Temporary safety measures are in place while an EU review investigates the link between cases of serious liver injury, including 4 cases requiring liver transplantation, and Esmya for uterine fibroids.

Advice for healthcare professionals:

- do not initiate new treatment courses of Esmya, including in women who have completed one or more treatment courses previously
- perform liver function tests at least once a month in all women currently taking Esmya and again 2–4 weeks after stopping treatment.
- check transaminase levels immediately in current or recent users of Esmya who present with signs or symptoms suggestive of liver injury (for example, nausea, vomiting, malaise, right hypochondrial pain, anorexia, asthenia, or jaundice)
- stop Esmya in any woman who develops transaminase levels more than 2-times the upper limit of normal, closely monitor and refer women for specialist hepatology evaluation as clinically indicated
- advise women using Esmya about the signs and symptoms of liver injury and tell them to seek immediate medical attention if they occur
- report suspected adverse drug reactions without delay to the [Yellow Card Scheme](#)

Review of liver safety

An EU-wide review of Esmya started in December 2017 following reports of serious liver injury in women using the medicine. The review is ongoing; however, temporary safety measures were introduced in February 2018 to protect women's health pending finalisation of the investigation. These measures were considered necessary following receipt of the fifth case of hepatic failure (the fourth that required liver transplantation).

We will provide further information as soon as the EU review is completed. Further information about the review can be found on the website of the [European Medicines Agency](#).

Healthcare professionals were informed of the temporary safety measures by the MHRA through a [notice on the Central Alerting System](#) and the Marketing Authorisation Holder has sent a [letter](#) to prescribers in the UK. The European Medicines Agency has issued information to both healthcare professionals and women, [available on their website](#).

To date, we have received 1 suspected adverse drug reaction report of hepatitis with the use of Esmya in the UK. Approximately 20,400 treatment courses of Esmya were dispensed in the UK between 1 October 2016 and 30 September 2017.¹

The emergency contraceptive ellaOne also contains ulipristal acetate (single-dose, 30 mg). No cases of serious liver injury have been reported with ellaOne and there are no concerns with this medicine at this time.

Background

Esmya was first authorised in 2012 for intermittent or pre-operative treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age. Each treatment course of 5 mg daily lasts for up to 3 months and may be repeated with breaks between each course.

Report suspected adverse drug reactions to Esmya

It is important that you report without delay any suspected adverse drug reactions associated with Esmya, including signs or symptoms of liver injury, to the [Yellow Card Scheme](#).

The Yellow Card Scheme is vital in helping the MHRA to monitor the safety of all healthcare products in the UK to ensure they are acceptably safe for patients and those that use them.

Article citation: Drug Safety Update volume 11 issue 8; March 2018: 2.

¹Data derived from IQVIA MIDAS 10/2016-09/2017 by MHRA, January 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.

Head lice eradication products: risk of serious burns if treated hair is exposed to open flames or other sources of ignition, eg, cigarettes

Pharmacists should tell people about the risk of fire when they discuss head lice eradication options.

Advice to pharmacists

- some products for the eradication of head lice infestations are combustible/flammable when on the hair and can ignite and cause serious harm in the presence of an open flame or other source of ignition such as when lighting cigarettes
- advise parents, caregivers and the person with head lice, if appropriate, that they should not smoke around treated hair and that it should be kept away from open flames or other sources of ignition, including in the morning after overnight application until hair is washed
- always advise parents and caregivers and the person with head lice to read the instructions that come with treatments to ensure that they are used safely and correctly
- report suspected adverse drug reactions, including burns, to the [Yellow Card Scheme](#)

Background

A range of products including Hedrin, Full Marks, and Nyda, are used for the eradication of head lice infestations.

Pharmacists are encouraged to help the person with head lice and their parents or caregivers to consider the advantages and disadvantages of each treatment option (see NHS Choices page on [Head lice and nits](#) and the [Head lice Clinical Knowledge Summary](#) from NICE for more information on options for eradication).

Cases of serious burns following combustion of hair

Eight cases of serious burns associated with Hedrin 4% cutaneous solution have been reported to the MHRA since the product was licensed in 2005. Following the first reported case in 2007, warnings about risk of fires were added to the pack and patient information leaflet for Hedrin 4% cutaneous solution. Four cases were associated with a cigarette lighter or lighting of a cigarette, one with a lit cigarette, one with a candle, and 2 with adjusting a gas fire.

There have been 2 further serious burns cases associated with other products. In 2006 a woman suffered serious burns when smoking during treatment. In 2017 another incident occurred when a child undergoing treatment came into contact with a naked flame, resulting in very serious burns.

Pharmacists should encourage parents, caregivers, and people with head lice to read the instructions carefully for all headlice eradication products.

Article citation: Drug Safety Update volume 11 issue 8; March 2018: 3.

Confidential prescribing and patient safety reports on key indicators now available free for GPs

Confidential reports designed to help you improve the quality of your prescribing and patient safety are now available for practices that contribute to the MHRA's Clinical Practice Research Datalink.

Information for GPs:

- GP practices can receive free quality improvement (QI) reports to enable:
 - patient-level case finding for contraindicated drug prescribing
 - easy review of individual patient care plans
 - confidential benchmarking against GP practices across the UK
 - collection of evidence for annual appraisals under [Good Medical Practice Domain 2 \(Safety and Quality\)](#)
- the reports are available to practices contributing de-identified patient data to Clinical Practice Research Datalink, a Centre of the MHRA (see About CPRD section below)

The Royal College of General Practitioners (RCGP) in conjunction with the MHRA's Clinical Practice Research Datalink (CPRD) have developed confidential bespoke practice and patient-level drug prescribing reports, available for free for GP practices contributing to CPRD.

The reports provide a list of pseudonymised patients at the practice so that GPs can re-identify and review their care plans. They also show the practice's prescription rate benchmarked against other participating GP practices.

Each report covers a selection of safety indicators. Current indicators are taken from the RCGP patient safety toolkit with input from NICE, including:

- Prescription of glitazones to patients with heart failure
- Prescription of non-steroidal anti-inflammatory drugs (NSAIDs) to patients with heart failure
- Prescription of NSAIDs to patients with chronic kidney disease (CKD)
- Aspirin monotherapy for stroke prevention in patients with atrial fibrillation

GPs are invited to take an active role in suggesting topics for future reports.

A sample report is available on the [CPRD website](#). Dr Tommy Hunter has written a [blog](#) about how he has used the report at his own practice. Unlike much of the performance measurement information that a practice receives, this report is for practice-use only and not in the public domain.

To receive the reports, practices must first [join CPRD](#).

About CPRD

CPRD is a Centre of the MHRA and jointly supported by the National Institute for Health Research (NIHR). CPRD provides access to anonymised UK health data for public health research. Research using CPRD data has resulted in over 1,800 publications which have led to improvements in drug safety, best practice, and clinical guidelines. The data are also used by the MHRA, in conjunction with the [Yellow Card Scheme](#), to support the continuous monitoring of the safety of medicines and vaccines. To find out more about CPRD and the other benefits of joining, visit the [CPRD website](#).

Further information

For more information about the new reports, please contact the RCGP lead for this project, David Mullett at david.mullett@rcgp.org.uk.

Article citation: Drug Safety Update volume 11 issue 8; March 2018: 4.

Letters sent to healthcare professionals in February 2018

In February 2018, the following letters were sent to relevant healthcare professionals:

- ellaOne post-marketing surveillance: [pregnancy registry](#)
- Ocaliva ▼ (obeticholic acid): [reinforced differential dosing recommendations in primary biliary cholangitis \(PBC\) patients with moderate and severe hepatic impairment](#)
- ERWINASE: [vials from batch 186G* should be used with a 5-micron filter needle](#)
- Bleo-Kyowa (bleomycin sulphate), powder for solution for injection – [use 5-micron filter during IV infusion or pre-injection](#) – see [Class 4 Medicine Defect Information alert](#)
- Velcade (bortezomib) 3.5 mg vials: [potential defect of rotating and/or loose metal cap](#)
- Restrictions on the use of ulipristal acetate, Esmya 5 mg tablet, and [important new warnings of serious liver injury and recommendations for liver monitoring](#)
- Eperzan ▼ (albiglutide): [reminder letter regarding discontinuation](#)

Article citation: Drug Safety Update volume 11 issue 8; March 2018: 5.

Medical Device Alerts issued in February 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](#).

Alert were recently issued by MHRA about:

- [Recall of specific lots of RUSCH sensor \(series 400\) silicone and non-sterile rectal/pharyngeal temperature sensors](#)
- [Aquilon series of nebulisers – CE mark withdrawn and supply ceased](#)

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