

# 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

Volume 11 Issue 9 April 2018

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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.

First, we bring you very important regulatory guidance following a EU-wide review into the significant harms from use of valproate medicines in pregnancy (page 2). Read and act promptly on the new measures to ensure all women and girls on valproate are informed of the risks and meet the conditions of the Pregnancy Prevention Programme.

Next, read about the importance of following recommended dose reductions according to liver function monitoring in patients with pre-existing moderate or severe liver impairment who are taking obeticholic acid (Ocaliva ▼) for primary biliary cholangitis and whose liver function declines (page 6).

Finally, we remind you that all healthcare professionals, including students, can use the Yellow Card Scheme to report suspected adverse reactions. On page 7, read about changes to fields on the Yellow Card website that help healthcare professionals to add further details about their occupation when submitting a concern.



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/](http://www.evidence.nhs.uk/)

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## **Valproate medicines (Epilim ▼, Depakote ▼): contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met**

Valproate medicines must no longer be used in women or girls of childbearing potential unless a Pregnancy Prevention Programme is in place. Ensure all women and girls (and their parent, caregiver, or responsible person, if necessary) are fully informed of the risks and the need to avoid exposure to valproate medicines in pregnancy.

### **Advice for healthcare professionals:**

#### **New contraindication unless Pregnancy Prevention Programme in place**

- valproate medicines must not be used in women and girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met (see below) and only if other treatments are ineffective or not tolerated, as judged by an experienced specialist
- you will receive materials by post in the coming weeks to use in the implementation of the Pregnancy Prevention Programme (Patient Guide, Healthcare Professional Guide, Risk Acknowledgement Form, and, for pharmacists, Patient Cards and stickers to attach a warning label to the pack)
- GPs must identify and recall all women and girls who may be of childbearing potential, provide the Patient Guide and check they have been reviewed by a specialist in the last year and are on highly effective contraception (see later for information on contraception)
- specialists must book in review appointments at least annually with women and girls under the Pregnancy Prevention Programme and re-evaluate treatment as necessary; explain clearly the conditions as outlined in the supporting materials; and complete and sign the Risk Acknowledgement Form—copies of the form must be given to the patient or patient/caregiver/responsible person and sent to their GP

#### **Action for pharmacists**

- ensure valproate medicines are dispensed in whole packs whenever possible — all packs dispensed to women and girls of childbearing potential should have a warning label either on the carton or via a sticker (see later for more about Warnings added to packs)
- discuss risks in pregnancy with female patients each time you dispense valproate medicines and ensure they have the patient guide and have seen their GP or specialist to discuss their treatment and the need for contraception

#### **Contraindication in pregnancy**

- use of valproate medicines in pregnancy is contraindicated for bipolar disorder and must only be considered for epilepsy if there is no suitable alternative treatment

#### **Act on and report any concerns about adverse pregnancy outcomes**

- report any suspected adverse reactions associated with valproate, including adverse pregnancy outcomes, to the [Yellow Card Scheme](#)

### **Teratogenicity of valproate medicines**

Valproate medicines are indicated for the treatment of epilepsy and bipolar disorder. Epilim ▼ and Depakote ▼ are the most commonly dispensed valproate medicines in the UK. Other brands available are Convulex ▼, Episenta ▼, Epival ▼, Kentlim ▼, Orlept ▼, Syonell ▼, and Valpal ▼.

1 Meador K, et al. [Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years \(NEAD study\): a prospective observational study.](#) *Lancet Neurol* 2013; 12: 244–52.

2 Christensen J, et al. [Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism.](#) *JAMA* 2013; 309: 1696–703.

3 Veiby G, et al. [Exposure to antiepileptic drugs in utero and child development: a prospective population-based study.](#) *Epilepsia* 2013; 54: 1462–72.

4 Cohen MJ, et al. [Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6 years.](#) *Epilepsy Behav* 2013; 29: 308–15

5 Bromley RL, et al. [Early cognitive development in children born to women with epilepsy: a prospective report.](#) *Epilepsia* 2010; 51: 2058–65.

6 Cummings C, et al. [Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine.](#) *Arch Dis Child* 2011; 96: 643–47.

7 Meador KJ, et al. [Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs.](#) *NEJM* 2009; 360: 1597–605.

8 Thomas SV, et al. [Motor and mental development of infants exposed to antiepileptic drugs in utero.](#) *Epilepsy Behav* 2008; 229–36.

9 Bromley R, et al. [Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child.](#) *Cochrane Database Syst Rev* 2014, Issue 10.

10 [Valproate and risk of abnormal pregnancy outcomes: new communication materials.](#) Drug Safety Update. 17 February 2016.

11 [Valproate and developmental disorders: new alert asking for patient review and further consideration of risk minimisation measures.](#) Drug Safety Update. 24 April 2017.

12 NHS England. [Data for prescribing of sodium valproate.](#) Accessed March 2018.

13 Epilepsy Action. [Almost one-fifth of women taking sodium valproate for epilepsy still not aware of risks in pregnancy, survey shows.](#) Accessed March 2018.

Valproate is highly teratogenic and evidence supports that use in pregnancy leads to [physical birth defects](#) in 10 in every 100 babies (compared with a background rate of 2 to 3 in 100) and neurodevelopmental disorders in approximately 30 to 40 in every 100 children born to mothers taking valproate.<sup>1,2,3,4,5,6,7,8,9</sup>

Due to the teratogenic risk, valproate medicines should not be used in girls and women of childbearing potential unless there is no suitable alternative as judged by a specialist experienced in the management of epilepsy or bipolar disorder. The National Institute for Health and Care Excellence (NICE) has updated guidelines relevant to valproate medicines to reflect the regulatory changes.

Previous communications<sup>10,11</sup> about the risk of neurodevelopmental disorders and the recommendation that women and girls of childbearing potential use effective contraception had little impact on prescribing.<sup>12</sup> Data from the [Clinical Practice and Research Datalink](#) show that pregnancies continue to be exposed to valproate medicines. Additionally, patients have reported that they still are not receiving the necessary information to make an informed decision in many cases.<sup>13</sup>

### **New regulatory measures for valproate medicines**

In March 2017, a EU scientific review examined the available evidence relating to the effectiveness of previous regulatory action and consulted widely with healthcare professionals and with patients. The review has now recommended [new measures](#) to avoid valproate exposure in pregnancy (see below).

An alert has been issued by the Chief Medical Officer to healthcare professionals in England to inform them of the importance of acting on these new prescribing and dispensing requirements. This will be followed by messages to healthcare professionals from the Chief Medical Officers of Scotland, Wales, and Northern Ireland. Letters will also be sent directly to healthcare professionals to inform them of the new measures.

### **Conditions and guidance for the Pregnancy Prevention Programme**

All women and girls of childbearing potential being treated with valproate medicines must be supported on a Pregnancy Prevention Programme. These conditions are also applicable to female patients who are not sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The Pregnancy Prevention Programme is a system of ensuring all female patients taking valproate medicines:

- have been told and understand the risks of use in pregnancy and have signed a Risk Acknowledgement Form
- are on highly effective contraception if necessary
- see their specialist at least every year

Conditions of the Pregnancy Prevention Programme for valproate are consistent with programmes available for other highly teratogenic drugs such as [thalidomide](#) and [isotretinoin](#).

The Pregnancy Prevention Programme is supported by the following, which have been revised to be consistent with the new requirements:

- **A Patient Guide** – to be provided to girls (of any age) and women of childbearing potential (or their parent/caregiver/responsible person) who are started on or are continuing to use valproate medicines
- **A Guide for Healthcare Professionals** – for guidance to all prescribers, pharmacists, and other healthcare providers involved in the care of women and girls of childbearing potential using valproate medicines
- **A Risk Acknowledgement Form** – for the specialist and patient (or their parent/caregiver/responsible person) to sign at initiation and at treatment reviews at least every year. The patient should receive a copy of the form; one copy should be filed in the specialist notes, and one copy sent to the patient's GP
- **A Patient Card** – to be given by pharmacists to all female patients who are dispensed valproate medicines to inform them of the risks
- **Stickers with warning symbols** – for pharmacists to add to the packaging of valproate medicines (see below for more about Warnings added to packs)

Hardcopies of these materials will be sent to healthcare professionals by the Epilim licence holder shortly. We will update this article online and the [MHRA Valproate guidance page](#) once they are available online.

To support these materials, the MHRA, in collaboration with professional and patient groups, has produced a [patient information sheet \(large print version\)](#) to help you discuss the new measures with patients, and their parents/caregivers/responsible person if appropriate.

### **Contraception and pregnancy prevention**

As with all teratogenic medicines, pregnancy should be excluded before initiation on valproate medicines with a negative plasma pregnancy test, confirmed by a healthcare professional.

Women and girls of childbearing potential must use highly effective contraception if they are able to become pregnant (see [guidance](#) from Faculty of Sexual and Reproductive Health [FSRH]). Methods of contraception considered 'highly effective' in this context include the long-acting reversible contraceptives (LARC): copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS), and progestogen-only implant (IMP), and male and female sterilisation, all of which have a failure rate of less than 1% with typical use (see guidance from FSRH for [more about user-independent methods and failure rates](#)). If a user-independent form is not used, two complementary forms of contraception including a barrier method should be used and regular pregnancy testing considered.

Individual circumstances should be, in each case, evaluated when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures.

At initiation and at a review at least every year, specialists should discuss the risks of valproate in pregnancy and complete and sign the Risk Acknowledgement Form with the patient (or their parent/caregiver/responsible person). This is to record that they have discussed and understood the risks and have been fully informed on the need to use highly effective contraception, without interruption, during the entire duration of treatment with valproate.

### **Warnings added to the packaging of valproate medicines**

A visual warning symbol will be added to the carton of valproate medicines by September 2018. This symbol will show a pregnant woman in a red circle with a line through it, with warning text about the risks and information about the new measures.

Pharmacists should therefore dispense in whole packs whenever possible. This will ensure that patients always see the warning symbol and receive the statutory information. If you must split a pack, or if the carton does not have a symbol on it, warning labels should be added to the box – stickers will be available with the educational materials to be sent to pharmacists by post.

Pharmacists should give the patient card to female patients when dispensing valproate. Packs of valproate medicines will start to be available with a detachable patient card from December 2018.

If a woman or girl of childbearing potential reports that she is not taking effective contraception, pharmacists should advise her to contact her GP for an urgent follow-up.

### **Audit functions and prescribing alerts in GP software**

NHS Digital has asked GP systems suppliers to provide a search and audit function to allow GPs to identify women on valproate medicines. Prescribing alerts for valproate medicines will also be updated with reminders of the responsibilities of prescribing GPs in line with the regulatory position. NHS Digital has also worked with community pharmacy dispensing system suppliers so that alerts are shown when prescriptions are dispensed.

### **New contraindication in pregnancy**

The strengthened regulatory position includes a new absolute contraindication for use of valproate medicines in pregnancy for the bipolar disorder indication. In the epilepsy indication, the contraindication for use in pregnancy applies unless there are no suitable alternatives, recognising that in some patients who are already pregnant switching antiepileptic medicines may not be feasible. In this case, access to counselling about the risks should be provided (see Healthcare Professional Guide for more information) and the Risk Acknowledgement Form signed by both specialist and patient.

### **Further information**

[Guidance. Valproate use by women and girls.](#) 23 March 2018.

*Article citation: Drug Safety Update volume 11 issue 9; April 2018: 1.*

## **Obeticholic acid (Ocaliva ▼): risk of serious liver injury in patients with pre-existing moderate or severe hepatic impairment; reminder to adjust dosing according to liver function monitoring**

We are aware of reports of serious liver injuries and deaths in patients with primary biliary cholangitis with pre-existing moderate or severe liver impairment who were not adequately dose-adjusted. Follow dose reduction and monitoring advice in these patients to reduce the risk of serious liver injury.

### **Advice for healthcare professionals:**

- patients with pre-existing moderate or severe liver impairment who are taking obeticholic acid are at risk of serious liver injury; adequate dose reduction in these patients is therefore essential
- assess hepatic status before starting obeticholic acid
- start patients with Child-Pugh Class B or C or decompensated liver cirrhosis at a reduced dose of 5 mg once a week (rather than once a day) and only increase dosing frequency to 5 mg twice a week (at least 3 days apart) and subsequently 10 mg twice a week (at least 3 days apart) in these patients if an adequate reduction in alkaline phosphatase and/or total bilirubin has not been achieved after 3 months and if the patient is tolerating the medicine – see [Summary of Product Characteristics](#)
- monitor all patients for primary biliary cholangitis (PBC) progression with laboratory and clinical assessment and evaluate at regular intervals the need for dose reduction
- report any suspected adverse drug reactions to obeticholic acid via the [Yellow Card Scheme](#)

### **Background**

Obeticholic acid (Ocaliva ▼) is a farnesoid X receptor (FXR) agonist. It is indicated in the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

### **Liver-related adverse events**

An EU review assessed reports of serious liver injuries and deaths in patients with primary biliary cholangitis with pre-existing moderate or severe liver impairment who were not adequately dose-adjusted. Liver-related adverse events have occurred both early in treatment and after months of treatment. Most cases were in the USA, but cases have also been reported in Europe.

The review concluded that no changes to the product information were required but suggested that healthcare professionals should be reminded of the dosing recommendations. A [letter](#) has also been sent to prescribers.

[Direct  
Healthcare  
Professional  
Communication.  
Ocaliva.](#)  
February 2018.

We have received 2 Yellow Card reports of hepatobiliary disorders in the UK associated with obeticholic acid. Neither case was fatal, but one case was life-threatening and required hospital admission and the other case led to discontinuation of therapy.

Hepatic status should be determined before starting treatment with obeticholic acid. Hepatically-impaired patients should receive a reduced starting dose of 5 mg once weekly in line with the recommendations in section 4.2 of the [Summary of Product Characteristics](#) for Ocaliva ▼.

### **Call for reporting**

Obeticholic acid (Ocaliva ▼) is subject to additional monitoring, allowing quick identification of new safety information. Report any suspected adverse drug reactions to the [Yellow Card Scheme](#).

*Article citation: Drug Safety Update volume 11 issue 9; April 2018: 2.*

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### **Suspect an adverse reaction? Yellow Card it!**

#### **Anyone can report a Yellow Card**

The Yellow Card Scheme is the UK system for monitoring the safety of medicines and healthcare products to ensure that they are acceptably safe for use by patients. Reporting to the Scheme is voluntary and relies upon the identification and reporting of suspected adverse drug reactions by healthcare professionals and patients – only a suspicion is needed to report a Yellow Card.

Patients, caregivers, and all healthcare professionals, including students, are encouraged to report any suspected adverse drug reactions to the Yellow Card Scheme. Following feedback from reporters, the [reporting website](#) has been updated so that if your occupation is not in the drop-down list, you can now select 'Other healthcare professional' and tell us more about your role in a free-text field.

All Yellow Card reports are systematically analysed and often result in identification of important new drug safety issues and changes to advice for healthcare professionals and patients.

#### **What to report?**

Yellow Cards can be used for reporting suspected adverse drug reactions to medicines, vaccines, herbal, or complementary products, whether self-medicated or prescribed. This includes suspected adverse drug reactions associated with misuse, overdose, medication errors, or from use of unlicensed and off-label medicines.

**Graph showing the number of direct ADR reports received from various healthcare professionals over the last 5 years.**

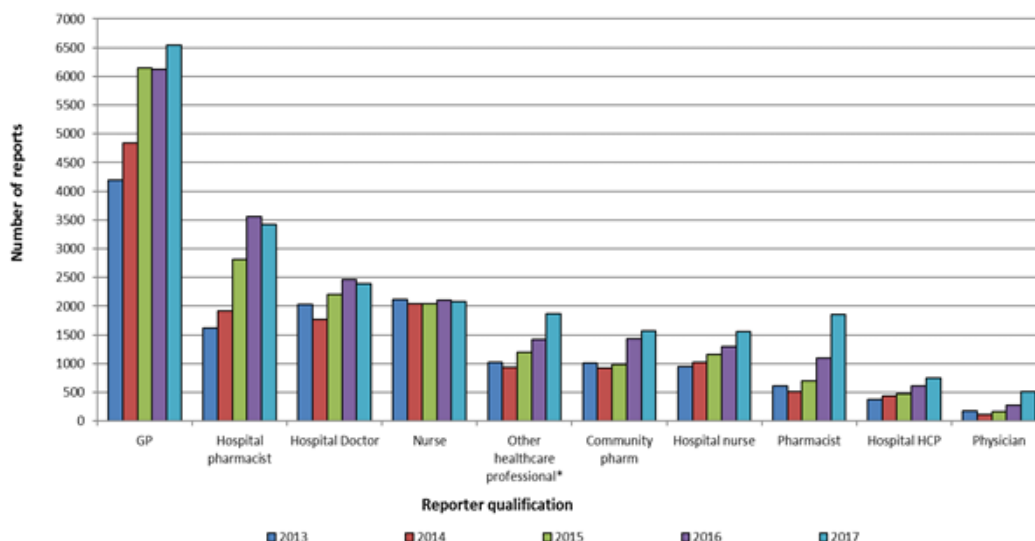


Figure 1: Graph showing the number of direct ADR reports received from various healthcare professionals over the last 5 years. \*Other health professionals include: dentists, optometrists, coroners, healthcare assistants, paramedics, chiropractors, medical students and other non-specified health professionals. ADR=adverse drug reaction.

You should report all suspected adverse drug reactions that are:

- Serious, medically significant or result in harm. Serious events are fatal, life-threatening, a congenital abnormality, disabling or incapacitating, or resulting in hospitalisation
- associated with newer drugs and vaccines (▼), irrespective of whether they are serious or not; the most up-to-date list of black triangle medicines is available [on the MHRA website](#)

If in doubt as to whether to report a suspected adverse drug reaction, please complete a Yellow Card. Please do not assume someone else has reported it. Your Yellow Card report makes a difference to improving patient safety.

### It's quick and easy to report

You can report Yellow Cards for all medicines, medical device adverse incidents, defective medicines, counterfeit or fake medicines or medical devices, and safety concerns with e-cigarettes or their refill containers on the [Yellow Card website](#).

You can also report suspected adverse reactions to medicines:

- via the free Yellow Card app; download now from the [Apple App Store](#) or [Google Play Store](#)
- Through some clinical IT systems (SystemOne/Vision/MiDatabank)
- By phone: 0800 731 6789 (freephone number, 10am to 2pm Monday-Friday).
- Using forms in the BNF, MIMS, or PAGB OTC directory
- By downloading forms from the Yellow Card website and sending them freepost to 'Yellow Card'

More information for healthcare professionals can be found on the [MHRA website](#)

Article citation: *Drug Safety Update* volume 11 issue 9; April 2018: 3.



## Letters sent to healthcare professionals in March 2018

In March 2018, letters were sent to healthcare professionals about:

- [Zinbryta ▼ \(daclizumab beta\): Marketing authorisation suspended in the European Union](#) – for more information see [Drug Safety Update March 2018](#)
- [Recall of specific batches of Lynparza 50mg capsules](#)
- [Radium-223-dichloride \(Xofigo\) contraindicated in combination with abiraterone acetate \(Zytiga\) and prednisolone/prednisone](#) – for more information see [Drug Safety Update December 2017](#)

*Article citation: Drug Safety Update volume 11 issue 9; April 2018: 4.*

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## Medical Device Alerts issued in March 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](#).

An alert was recently issued by MHRA about:

- [All T34 ambulatory syringe pumps – risk of unintended pump shutdown and delay to treatment](#)

*Article citation: Drug Safety Update volume 11 issue 9; April 2018: 5.*

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