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.

Published 24 April 2018

From:
Medicines and Healthcare products Regulatory Agency (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency)

Therapeutic area:
Anaesthesia and intensive care (https://www.gov.uk/drug-safety-update?therapeutic_area%5B%5D=anaesthesia-intensive-care), Neurology (https://www.gov.uk/drug-safety-update?therapeutic_area%5B%5D=neurology), Obstetrics, gynaecology and fertility (https://www.gov.uk/drug-safety-update?therapeutic_area%5B%5D=obstetrics-gynaecology-fertility), Paediatrics and neonatology (https://www.gov.uk/drug-safety-update?therapeutic_area%5B%5D=paediatrics-neonatology), Psychiatry (https://www.gov.uk/drug-safety-update?therapeutic_area%5B%5D=psychiatry)

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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 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 (https://yellowcard.mhra.gov.uk/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▼.

Valproate is highly teratogenic and evidence supports that use in pregnancy leads to physical birth defects (https://rarediseases.org/rare-diseases/fetal-valproate-syndrome/) 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. [1] [2] [3] [4] [5] [6] [7] [8] [9]

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[10] [11] about the risk of neurodevelopmental disorders and the recommendation that women and girls of childbearing potential use effective contraception had little impact on prescribing.[12] Data from the Clinical Practice and Research Datalink (https://www.cprd.com/home/) 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.[13]

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 (https://www.gov.uk/government/news/new-measures-to-avoid-valproate-exposure-in-pregnancy) to avoid valproate exposure in pregnancy (see below).

An alert (https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102736) 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 (https://www.medicines.org.uk/emc/product/6317) and isotretinoin (https://www.medicines.org.uk/emc/product/8558).

The Valproate 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 and the MHRA Valproate Guidance (https://www.gov.uk/guidance/valproate-use-by-women-and-girls) once they are available online.

To support these materials, MHRA, in collaboration with professional and patient groups, has produced a patient information sheet (https://assets.publishing.service.gov.uk/media/5ade0039e5274a0d820946a6/Valproate-patient-DSU-for-pub-without-watermark.pdf) (large print version available (https://assets.publishing.service.gov.uk/media/5ade004a40f0b60a9a9859d1/Valproate-patient-DSU-large-print-without-watermark.pdf)) to help you discuss the new measures with patients, and their parent/caregiver/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 (https://www.fsrh.org/news/fsrh-ceu-statement-on-contraception-for-women-using-known/) 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 (https://www.fsrh.org/documents/ukmec-2016/fsrh-ukmec-full-book-2017.pdf)). 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 a Risk Acknowledgement Form signed by both specialist and patient.

Further information

Guidance. Valproate use by women and girls (https://www.gov.uk/guidance/valproate-use-by-women-and-girls). 23 March 2018.

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

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Published 24 April 2018