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BY EMAIL

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Dear Colleague

MHRA Drug Safety Update – Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): New safety and educational materials to support regulatory measures in men and women under 55 years of age

The Medicines and Healthcare products Regulatory Agency (MHRA) have issued a Drug Safety Update, available at the following link.

New safety and educational materials have been introduced for men and women and healthcare professionals to reduce the harms from valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the risk of impaired fertility in males.

These safety and educational materials support the new regulatory measures announced in the National Patient Safety Alert.

Healthcare professionals should review the new measures and materials and integrate them into their clinical practice when referring patients and when prescribing or dispensing valproate.

The MHRA are also reviewing data highlighted in Drug Safety Update August 2023, which may suggest an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception. As a precaution the MHRA advise male patients who are planning a family within the next year, to discuss treatment options with a healthcare professional.

Valproate treatment and new safety measures

Advice for healthcare professionals:

- valproate must not be started in new patients (**male or female**) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. For the majority of patients, other effective treatment options are available
- at their next annual specialist review, women of childbearing potential and girls receiving valproate should be reviewed using the revised valproate Annual Risk Acknowledgement Form. A second specialist signature will be needed if the patient is to continue on valproate, however subsequent annual reviews will only require one specialist
- general practice and pharmacy teams should continue to prescribe and dispense valproate and if required offer patients a referral to a specialist to discuss their treatment options. Valproate should be dispensed in the manufacturer's original full pack
- report suspected adverse drug reactions associated with valproate on a Yellow Card

Advice for healthcare professionals to provide to patients:

- do not stop taking valproate without advice from a specialist. This is because epilepsy or bipolar disorder may worsen without treatment
- if you are on valproate, please attend any offered appointments to discuss your treatment plan and talk to a healthcare professional if you are concerned
- consult the Patient Information Leaflet and new Patient Guide for information about the risks of valproate – see also the MHRA information page for resources
- as a precaution, male patients who are planning a family within the next year should speak to a healthcare professional about their treatment options.

Exposure to valproate in pregnancy is associated with physical birth defects in 11% of babies and neurodevelopmental disorders in up to 30-40% of children, which may lead to permanent disability. Since 2018, valproate has been contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme (PPP) are followed.

In 2022, the Commission on Human Medicines (CHM) reviewed the latest data on the safety of valproate. The CHM heard from patients and other representatives about how valproate was being used and how the risks were currently managed. The CHM noted that data from the Medicine and Pregnancy Registry showed that pregnancies in England continue to be exposed to valproate.

The CHM also considered other known risks of valproate, including the risk of impaired male fertility. The CHM considered pre-clinical data on possible transgenerational risks with prenatal exposure, as well as data from studies in juvenile and adult animals suggesting adverse effects on the testes. There are currently limited data available on many of these risks in humans and further studies are planned. However, the CHM noted many patients receiving valproate have other therapeutic options with fewer potential reproductive harms.

On 28 November 2023, MHRA issued a National Patient Safety Alert to instruct Integrated Care Boards (in England), Health Boards (in Scotland), Health Boards (in Wales), and Health and Social Care Trusts (in Northern Ireland) to prepare for the new risk minimisation measures by 31 January 2024. The new safety and educational materials support these measures.

Due to the known significant risk of serious harm to a baby after exposure to valproate in pregnancy, these measures aim to ensure valproate is only used if other treatments are ineffective or not tolerated, and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme (PPP).

The CHM will consider further recent registry data which may suggest an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception. In the study, around 5 children in 100 born to fathers treated with valproate around conception were diagnosed with a neurodevelopmental disorder. This is compared to 3 in 100 children whose fathers were taking lamotrigine or levetiracetam around conception (two other anti-seizure medicines). As a precaution male patients on valproate who are planning a family within the next year should speak to a healthcare professional about their treatment options.

See the MHRA Public Assessment Report and MHRA website, which will be added to in the coming weeks and months. The MHRA review of antiepileptic drugs in pregnancy should also be consulted.

New Regulatory Safety and Educational Materials

To support the implementation of the new measures for valproate, the following safety and educational materials are being made available:

- Updated Healthcare Professional Guide: Provides updated information for healthcare professionals on the risks of valproate in pregnancy and the risks for male patients, the new conditions for valproate prescribing and key points for patient discussions.

- Updated Patient guide: Provides those taking valproate (or their parent, caregiver, or responsible person) with updated information on the risks of valproate in pregnancy and the risks to male patients and what they need to do.

- Updated Annual Risk Acknowledgement Form: For female patients starting valproate and at annual review. Used to support and record the discussion between the patient and specialist prescriber on the risks associated with valproate in pregnancy and to record the decision of the countersigning specialist. At subsequent annual reviews only one specialist is required.

- New Risk Acknowledgement Form for male patients starting valproate: Used to support and record the discussion between the patient and specialist prescriber of the risks associated with valproate in males when starting treatment with valproate and to record the decision of the countersigning specialist. This is only to be completed at initiation of valproate.

- Patient card: Provides key information for female patients receiving valproate on contraception and pregnancy prevention.

- Pharmacy poster: Provides important actions for pharmacists dispensing valproate to female patients.

- Warning stickers: To be added to packaging of medicine in exceptional circumstances where the original pack cannot be dispensed.

The updated product information and safety and educational materials are available on the MHRA website and the electronic Medicines Compendium. Links to the patient guide and patient card are also available via a QR code provided in the Patient Information Leaflets for Epilim and Depakote. The Marketing Authorisation Holders are sending a letter to healthcare professionals to support these changes with the hard copies of the materials which will begin distribution next week. On receipt of the new materials, healthcare professionals should discard previous versions of the valproate materials.

Further materials to support discussions with patients

Patients on valproate must be fully informed of the potential risks and counselled on their treatment options at the time of initial prescribing and at all subsequent reviews.

The MHRA ask clinicians to use appropriate individualised language when discussing the implications of taking valproate with patients and their caregivers.

The safety and educational materials should be used alongside other resources to support patients making decisions about valproate and other treatments for epilepsy and bipolar disorder. These include patient support tools, such as those published by the NHS and guidelines produced by the Association of British Neurologists.

Report suspected reactions on a Yellow Card

Valproate is a black triangle medicine, and all suspected adverse reactions should be reported via the Yellow Card scheme. Reports can be made of suspected reactions experienced at any time, including historic adverse experiences with medicines.

Please include in the report as much detail as possible, particularly if a side effect continued or started after treatment was stopped. Information about medical history, any concomitant medication, onset timing, treatment dates, and product brand name should also be included.

Report to the Yellow Card scheme electronically using::

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals

The complete MHRA Drug Safety update is available at the following link.

Yours sincerely

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Chief Medical Officer

Professor Cathy Harrison
Chief Pharmaceutical Officer

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