The United Kingdom: Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): updated safety and educational materials to support patient discussion on reproductive risks

Medicines and Healthcare products Regulatory Agency (MHRA) announces that updated safety and educational materials are now available to support the implementation of the regulatory measures announced in the November 2023 National Patient Safety Alert and the September 2024 Drug Safety Update. They also include previous updates to product information on the risk of low birth weight in children exposed to valproate during pregnancy.

Advice for Healthcare Professionals:

- updated safety and educational materials are now available to support healthcare professionals and patients to implement the existing regulatory requirements
- the updates reflect:
    - precautionary advice on the potential risk of neurodevelopmental disorders in children fathered by men taking valproate around the time of conception
    - a risk of lower weight at birth for the gestational age in children exposed to valproate during pregnancy
- healthcare professionals should review the new materials and integrate them into their clinical practice when referring patients and when prescribing or dispensing valproate

As a reminder

- 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
- valproate must not be prescribed to any woman or girl able to have children unless the conditions of the Pregnancy Prevention Programme (PPP) are followed
- as a precaution, recommend that male patients use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate, to allow for one completed sperm cycle not exposed to valproate. For further information see the September 2024 Drug Safety Update

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
- women and girls who are able to have children and who are taking valproate must follow the conditions of the Pregnancy Prevention Programme
- as a precaution it is recommended that male patients taking valproate should use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate
- 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. If you wish to discuss family planning, please contact a healthcare professional
- consult the Patient Information Leaflet and Patient Guide for men or Patient Guide for women for information about the risks of valproate – also the MHRA information page for information resources

Background

In September 2024, precautionary advice was communicated in Drug Safety Update on a potential risk of neurodevelopmental disorders in children fathered by men taking valproate around the time of conception. In February 2025, a Drug Safety Update communicated that review by two specialists remains in place for all patients initiating valproate under 55 years of age but the Commission on Human Medicines had advised that it will not be required for men (or males) currently taking valproate. Three infographics were published to clarify in which situations review by two specialists may be required:

- for female patients under 55 years old
- for male patients under 55 years old
- for male and female patients 55 years and older

Risk of lower weight at birth for gestational age

Product information has been updated to reflect epidemiological studies (please see references in 'Additional Information' section in the website in MHRA) which have reported a decrease in mean birth weight, and a higher risk of being born with a low birth weight (<2500 grams) or small for gestational age (defined as birth weight below the 10th percentile corrected for their gestational age, stratified by gender) for children exposed to valproate in utero in comparison to unexposed or lamotrigine-exposed children.

Updated safety and educational materials

Safety and educational materials have been updated in line with the current regulatory position and to reflect feedback from stakeholders.

The following new or updated safety and educational materials are now available online:

- Annual Risk Acknowledgement Form for female patients
- Risk Acknowledgement Form for male patients starting valproate
- Patient guide for women
- Patient guide for men
- Patient card
- Booklet for healthcare professionals
- Valproate dispensary poster

Please refer to the following website in MHRA for details:

http://www.gov.uk/drug-safety-update/valproate-belvo-convulex-depakote-dyzantil-epilim-epilim-chrono-or-chronosphere-episenta-epival-and-syonellv-updated-safety-and-educational-materials-to-support-patient-discussion-on-reproductive-risks

In Hong Kong, there are 10 registered pharmaceutical products containing valproate. All products are prescription-only medicines. So far, the Department of Health (DH) has received 17 cases of adverse drug reaction with regard to valproate, of which 2 cases were reported as congenital malformations following valproate exposure in utero, and these cases were not related to neurodevelopmental disorders in children after paternal exposure to valproate or low birth weight for children exposed to valproate in utero. Related news was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 2 Jul 2011, with the latest update posted on 7 Mar 2025. Letters to inform local healthcare professionals were issued by the DH on 4 Jul 2011, 7 May 2013, 13 Oct 2014, 12 Feb 2018, 13 Dec 2022 and 22 Mar 2023.

The Registration Committee of the Pharmacy and Poisons Board discussed the matter related to the risks in pregnancy associated with the use of valproate in Sep 2011, Dec 2014, Dec 2018 and Jun 2019. Currently, the package insert or sales pack label of locally registered valproate-containing products should include safety information on the risk of malformations and impaired cognitive development in children exposed to valproate during pregnancy, and contraindications, e.g. in women of childbearing potential unless pregnancy preventive measures have been implemented, etc. The certificate holders of locally registered valproate-containing products are also required to implement risk minimisation measures, e.g. patient information leaflet should be provided, etc.

In light of the above MHRA's announcement, letters to inform local healthcare professionals will be issued, and the matter will be further discussed by the Registration Committee of the Pharmacy and Poisons Board.

Ends/Wednesday, Jun 11, 2025
Issued at HKT 17:30