Valproate (Epilim▼, Depakote▼): NEW restrictions on use

PREGNANCY PREVENTION PROGRAMME to be put in place.

This letter is for **specialists and specialist nurses** managing patients treated with valproate medicines and **general practitioners** who provide primary care to these patients

Valproate medicines are sodium valproate [Epilim▼, Convulex▼, Episenta▼, Epival▼, Kentlim▼, Orlept▼, Valpal▼]; sodium valproate, valproic acid [Epilim Chrono/Chronosphere▼]; valproate semisodium [Depakote▼, Syonell▼]

Direct Healthcare Professional Communication

June 2018

Dear Healthcare Professional,

This letter is sent in agreement with the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) to inform you of **important new contraindications, strengthened warnings, and measures to prevent valproate exposure during pregnancy.**

Summary

- **Valproate should not be used in girls and women of childbearing potential** unless other treatments are ineffective or not tolerated, as judged by an experienced specialist.
- Children exposed to valproate in utero are at high risk of serious developmental disorders (in 30–40% of cases) and of congenital malformations (in approximately 10% of cases).
- **New contraindications apply:**
    - In epilepsy:
        - valproate is contraindicated in girls and women of childbearing potential, unless the conditions of **the valproate pregnancy prevention programme ("prevent"),** described in the documents enclosed, are met.
        - valproate is contraindicated in pregnancy unless there is no suitable alternative treatment.
    - In bipolar disorder:
        - valproate is contraindicated in girls and women of childbearing potential, unless the conditions of **the valproate pregnancy prevention programme ("prevent"),** described in the documents enclosed, are met.
        - valproate is contraindicated in pregnancy.
- In girls and women of childbearing potential currently using valproate, management will need to be re-evaluated to ensure that the conditions of **the valproate pregnancy prevention programme ("prevent"),** described in the documents enclosed, are met.

Educational materials

In order to assist healthcare professionals and patients to comply with the requirements of **the valproate pregnancy prevention programme ("prevent")**, revised educational materials have been produced. Included with this letter are the following materials:

- 1 copy of the *Guide for Healthcare Professionals* including prescribers, pharmacists, and other healthcare providers involved in the care of girls and women of childbearing potential using valproate medicines. **This contains full detail of the valproate pregnancy prevention programme ("prevent"), and should be read carefully.**
- 1 copy of the *Valproate Annual Risk Acknowledgement Form* for the prescriber to document that the patient has understood the risks in every annual visit. **This should be signed by the patient, then scanned and saved in her Patient Medical Record. A copy should be given to the patient and one copy sent to her GP.**
- 5 copies of the *Patient Guide* for the prescriber to **provide a copy to ALL girls and women of childbearing potential** who start treatment on valproate or who are continuing treatment with valproate but have not received a copy **of the May 2018 guide**, or no longer have it in their possession.

A Patient Card is also available for the pharmacist to provide to all female patients when dispensing valproate to them.

Additional copies of these materials can be ordered, free, by contacting Sanofi Medical Information on 0845 372 7101 or by emailing uk-medicalinformation@sanofi.com

The materials can also be downloaded from the EMC website (www.medicines.org.uk) where they will be found linked with entries for medicines containing valproate.

Copies of previous valproate educational materials, dated January 2016 or earlier, are now obsolete and should be discarded to prevent inadvertent use.

Background on the safety concern

In 2014 the warnings and restrictions on the use of valproate medicines in women and girls were strengthened, to minimise the risk of malformations and developmental problems in babies exposed to valproate in the womb. EMA's safety experts, the Pharmacovigilance Risk Assessment Committee (PRAC) have now reviewed the impact of these measures following concerns that the measures were not sufficiently effective in increasing awareness and reducing valproate use during pregnancy. The PRAC found these concerns to be well founded and have therefore introduced new measures.

Risk of abnormal pregnancy outcomes

Valproate is associated with a dose-dependent risk of abnormal pregnancy outcomes, whether taken alone or in combination with other medicines. Data suggest that when valproate is taken for epilepsy with other medicines, the risk of abnormal pregnancy outcomes is even greater than when valproate is taken alone. When valproate is taken alone:

- The risk of congenital malformations for children exposed in utero is approximately 10%, and studies in preschool children exposed in utero show that in 30–40%, early development, such as talking and walking, is delayed and they have low intellectual abilities, poor language skills, and memory problems.[1,2,3,4,5]

- Intelligence quotient (IQ) measured in a study of 6-year-old children with a history of valproate exposure in utero was on average 7–10 points lower than children exposed to other antiepileptics.[6]
- Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. [7]
- Limited data suggest that children exposed to valproate in utero may be more likely to develop symptoms of attention-deficit/hyperactivity disorder (ADHD).[8]

It is recommended that pregnant women taking antiepileptic drugs in general, and valproate in particular, are enrolled in the UK Epilepsy and Pregnancy Register (http://www.epilepsyandpregnancy.co.uk). This should be done as early in pregnancy as possible, and must be before any outcome of the pregnancy is known.

Call for reporting

All valproate medicines are subject to additional monitoring. Any suspected adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. You can also report suspected adverse events via the Yellow Card app available via the Apple App Store or Google Play Store. Adverse events should also be reported to the pharmaceutical company providing the valproate preparation.

Yours faithfully

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Consultant in Pharmaceutical Medicine, and
Medical Head – General Medicines, Sanofi UK

This letter is sent on behalf of all Marketing Authorisation Holders of Valproate containing products in the UK.

1. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010224.
2. Bromley RL, et al. Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 2010 October;51(10):2058–65.
3. CummingsC et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011;96:643–647.
4. Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. *NEJM* 2009;360(16):1597–1605.
5. Thomas SV et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy and Behaviour* 2008 (13):229–236.
6. Meador KJ, et al. NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013 12(3):244–252.
7. Christensen J et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013;309(16):1696–1703.
8. Cohen MJ et al. Fetal antiepileptic drug exposure: motor, adaptive and emotional/behavioural functioning at age 3 years. Epilepsy Behav. 2011; 22(2):240–246.