

## **Valproate (Epilim▼, Depakote▼): NEW restrictions on use: IMPORTANT ACTIONS FOR PHARMACISTS**

### **This letter is for all pharmacists dispensing valproate medicines**

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 Pharmacist,

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**

- 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)
- Valproate medicines 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
- In girls and women of childbearing potential **new contraindications** apply unless the conditions of **the valproate pregnancy prevention programme, called 'prevent'** are met.

#### **PHARMACISTS are asked to take the following IMPORTANT ACTIONS:**

- PROVIDE a Valproate Patient Card (dated May 2018) every time you dispense a valproate medicine to ALL female patients
- When dispensing any valproate preparation to female children, adolescents, women of childbearing potential, or pregnant women CHECK that their prescriber has discussed the risks of exposure in pregnancy with them and they are aware of these and subsequently they are taking EFFECTIVE CONTRACEPTION unless already pregnant.
- If the prescriber HAS NOT DISCUSSED the risk with the patient or the patient is not taking effective contraception, tell them to CONTACT their GP or specialist for an urgent follow-up.
- Advise the patients NOT TO STOP valproate medication and to immediately contact their GP or specialist in case of suspected pregnancy.
- ASK if they have received an updated Valproate Patient Guide (dated May 2018) and provide a copy if they have not received this or no longer have it in their possession.
- Dispense valproate in the ORIGINAL PACKAGE with the outer warning and avoid repacking. In the situations where this cannot be avoided, always provide a copy of the package leaflet, patient card, and add a warning sticker to the outer box.
- Please ensure you cascade this important information to all dispensary staff.

## **Educational Materials**

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, **revised** educational materials have been produced. Included in 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.**

- 2 packs of 10x Patient Cards to provide a card to all female patients when dispensing valproate to them.

- 5 copies of the *Patient Guide* to provide to all female patients who have not received a copy (dated May 2018) or no longer have it in their possession.

- 5 sheets of 14x Warning Stickers – to be used if valproate is dispensed out of its original packaging

- 1 A4 poster for display in the dispensary area to remind pharmacy staff of these requirements.

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

The materials can also be downloaded from the EMC website ([www.medicines.org.uk](http://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.<sup>1,2,3,4,5,</sup>
- 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.<sup>6</sup>
- 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.<sup>7</sup>

- Limited data suggest that children exposed to valproate in utero may be more likely to develop symptoms of attention-deficit/hyperactivity disorder (ADHD) <sup>8</sup>

### 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](http://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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**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. Cummings C 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.* 2001; 22(2):240–246.