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IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

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Valproate - containing medicines: new measures regarding the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception

Dear Healthcare professional,

This letter is sent in agreement with the European Medicines Agency (EMA) and the Health Products Regulatory Authority to inform you of the following:

Summary

- **A retrospective observational study in 3 Nordic countries suggests an increased risk of neurodevelopmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy. Due to study limitations, this risk is possible but is not confirmed.**

New measures for valproate use in male patients

- **It is recommended that in male patients valproate is initiated and supervised by a specialist experienced in treatment of epilepsy or bipolar disorder.**
- **Prescribers should inform male patients about the potential risk and discuss with them the need to consider effective contraception, including for a female partner, while using valproate and for 3 months after stopping the treatment;**
- **Treatment with valproate in male patients should be regularly reviewed by prescribers to evaluate whether valproate remains the most suitable treatment for the patient.**
- **For male patients planning to conceive a child, suitable alternative treatment options should be considered and discussed with the patient. Individual circumstances should be evaluated for each patient. It is recommended that advice from a specialist experienced in the management of epilepsy or bipolar disorder should be sought as appropriate.**
- **The male patients should be advised to not donate sperm during treatment and for at least 3 months after treatment discontinuation.**
- **A patient guide should be provided to male patients.**

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Background on the safety concern

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has evaluated data from a study (EUPAS34201) conducted by pharmaceutical companies of valproate containing products as an obligation following a previous EU-wide review of valproate use during pregnancy. The primary objective was to investigate the risk of NDDs in offspring paternally exposed to valproate as monotherapy, compared to lamotrigine or levetiracetam as monotherapy treatment, in the 3 month period prior to conception. This retrospective observational study was conducted using data from multiple registry databases in Denmark, Sweden and Norway. The primary outcome of interest was NDDs (composite endpoint including autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders, movement disorders) in offspring up to 11 years of age. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group.

- The meta-analysis of data from the 3 countries resulted in a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07) for NDDs in children from fathers treated with valproate monotherapy in the 3 months prior to conception compared to the composite lamotrigine/levetiracetam monotherapy group.
- The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group monotherapy versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy group.

The study was not large enough to investigate associations with specific NDD subtypes. Due to study limitations, including potential confounding by indication and differences in follow-up time between exposure groups, the risk of NDDs in children of fathers that used valproate in the 3 months prior to conception is considered a potential risk and a causal association with valproate is not confirmed.

The study did not evaluate the risk of NDD to children born to men who had discontinued valproate treatment for more than 3 months before conception (i.e., allowing a new spermatogenesis without valproate exposure).

The observed potential risk of NDDs after paternal exposure in the 3 months before conception is of lower magnitude than the known risk for NDDs after maternal exposure during pregnancy. When valproate is administered as monotherapy to women, studies in pre-school children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Based on the available data, new measures for valproate use in men have been adopted as specified in the "summary" above. The product information of all valproate-containing medicines is being updated to inform healthcare professionals and patients of the potential risk of NDD in children of men treated with valproate and to provide guidance regarding use of valproate in men. In addition, educational materials will be available for healthcare professionals and male patients. These include:

- An updated guide for healthcare professionals with a dedicated section on the use of valproate in male patients;
- A new patient guide for males, which should be provided to male patients using valproate;
- An update of the existing patient card with the information for male patients, attached to the outer packaging, so that it will be provided in the pharmacy to the patient each time the medicine is dispensed.

Call for reporting

Valproate (Epilim▼) is subject to additional monitoring.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie

Adverse events should also be reported to Sanofi Ireland Ltd. Tel: 01 403 5600. Alternatively, send via email to IEPharmacovigilance@sanofi.com.

Company contact point

Should you have any questions or require additional information, please contact Medical Information Department at IEmedinfo@sanofi.com or by phone on 01 403 5600.

Yours faithfully,

R Grundy

Rod Grundy

Senior Medical Advisor Sanofi UK & Ireland