By email only,

12th January 2024

Valproate: new precautionary measures for use in male patients following review of potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception

Dear colleague,

The Health Products Regulatory Authority (HPRA) wishes to inform you that the European Medicines Agency (EMA) announced today, 12th January, that its Pharmacovigilance Risk Assessment Committee (PRAC) have agreed new precautionary measures for the treatment of male patients with valproate medicines. These new measures are to address a potential increased risk of neurodevelopmental disorders in children born to men treated with valproate during the 3 months before conception.

A final regulatory position on these new measures is awaited from the EUs Heads of Medicines Agencies Co-ordination Group for Mutual recognition and Decentralised Procedures, Human (CMDh). Once made, the marketing authorisation holder (MAH) for valproate (Epilim) in Ireland will apply to the HPRA to change the terms of their marketing authorisations (licenses) in accordance with the PRAC recommendations, resulting in updates to the product information.

Following HPRA approval, a direct healthcare professional communication (DHPC) and educational materials will be distributed. It is anticipated that these regulatory steps will be completed over the next several weeks to months.

While these regulatory steps are ongoing, the HPRA wishes to inform healthcare professionals and patient organisations in Ireland of the review undertaken by the PRAC and of the new precautionary measures at the earliest opportunity. Further information is provided below.

Background

The PRAC has concluded its evaluation of 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 ongoing evaluation of this study was communicated previously by the HPRA.[1,2,3]

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.

- 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).

During its review, the PRAC also considered data from other sources, including non-clinical (laboratory) studies and scientific literature, and consulted patients and clinical experts in reaching its recommendations.

Based on the available data, new precautionary measures for valproate use in men will be introduced across all indications.

New precautionary measures for valproate use in men

- 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 should be sought as appropriate
- Male patients should be advised to not donate sperm during treatment and for at least 3 months after treatment discontinuation
- A patient guide and patient card will be made available*

**Information for patients on the outcome of the review and the new measures is currently available within the EMA's Public Health Communication, including advice that they should not stop their treatment without consulting their doctor. The HPRA website also now includes a link to this information.*

Educational materials and product information/packaging updates

Following HPRA approval, a direct healthcare professional communication will be distributed.

Educational materials will be available in due course, including an update to the existing guide for healthcare professionals to include a dedicated section on use in male patients, introduction of a new patient guide for men as well as inclusion of information in the existing patient card which is attached to the product carton. Product information (Summary of Product Characteristics (SmPC and Package Leaflet (PL)) will be updated to include details of the the study results and its limitations as well as the new precautionary measures.

The new measures come in addition to restrictions and other measures already in place to prevent exposure to valproate medicines in women during pregnancy due to the risk of congenital malformations (birth defects) and NDDs. The observed potential risk of NDDs after paternal exposure in the 3 months before conception is of lower magnitude than the confirmed risk for NDDs after maternal exposure during pregnancy.

We trust that you find the above update helpful. The HPRA would appreciate if this information could be cascaded to relevant colleagues, as appropriate.

Should you have any further queries, please submit these to medsafety@hpra.ie

Yours sincerely,

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Refs; 1. DHPC, 2. Drug Safety Newsletter, 3. Valproate (Epilim-) - EMA review of study in children whose fathers were treated with valproate (hpra.ie)