HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Valproate (Epilim ▼): New precautionary measures regarding the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months before conception

Key Message

- A retrospective observational study in three 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 three months before conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy. Due to study limitations, this risk is considered possible but has not been confirmed. As a precaution, new measures are being introduced to inform patients and healthcare professionals of this potential risk.
- 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 three months after stopping the treatment.
- Regularly review treatment in male patients 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.
- Male patients should be advised not to donate sperm during treatment and for at least three months after treatment discontinuation.
- It is recommended that in male patients, valproate is initiated and supervised by a specialist experienced in the treatment of epilepsy or bipolar disorder.

Background information

Valproate-containing medicines are approved nationally in Ireland with various presentations under the brand name Epilim for treatment indications in epilepsy and bipolar disorder*.

The HPRA previously published an article in Edition 113 of this newsletter regarding an ongoing review at that time by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) of a study to investigate the risk of neurodevelopmental disorders (NDDs) in offspring paternally exposed to valproate as monotherapy, compared to lamotrigine or levetiracetam as monotherapy treatment, in the three months before conception. At that time, the PRAC had requested the pharmaceutical companies involved in this study to provide re-analyses of corrected data, as some errors had been noted, as well as additional information and analyses to address study limitations. The PRAC has now completed its evaluation of the corrected data and has recommended new precautionary measures concerning the use of valproate in male patients.

The study (EUPAS34201[1]) was conducted by pharmaceutical companies of valproate-containing products as an obligation following a previous EU-wide review[2] of valproate use during pregnancy. This retrospective observational study used data from multiple registry databases in Denmark, Sweden and Norway[3,4]. The primary outcome of interest was NDDs (composite endpoint including autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders, and 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 three countries resulted in a pooled adjusted hazard ratio of 1.50 (95% CI: 1.09-2.07) for NDDs in children from fathers treated with valproate monotherapy in the three months before conception compared to the composite lamotrigine/levetiracetam monotherapy group.
- The adjusted cumulative risk of NDDs ranged between 4.0% and 5.6% in the valproate group monotherapy versus between 2.3% and 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 who used valproate in the three months before conception is considered a potential risk and a causal association with valproate is not confirmed. Nonetheless, considering the available data and consulting with stakeholders and experts, the PRAC considered precautionary measures warranted to inform patients and healthcare professionals[5,6].

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

The observed potential risk of NDDs after paternal exposure in the three months before conception is of a lower magnitude than the known risk for NDDs after maternal exposure during pregnancy. When valproate is administered as monotherapy to women, studies in preschool 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. A Direct Healthcare Professional Communication (DHPC) has also been sent to inform healthcare professionals of the review's outcome[7] and the new precautionary measures for male patients.

Advice for healthcare professionals

- 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 three months after stopping the treatment.
- Regularly review treatment with valproate in male patients 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.
- Male patients should be advised not to donate sperm during treatment and for at least three months after treatment discontinuation.
- It is recommended that in male patients, valproate is initiated and supervised by a specialist experienced in the treatment of epilepsy or bipolar disorder.

New educational materials for males

The PRAC's latest recommendations come in addition to restrictions and other measures already in place to avoid exposure to valproate during pregnancy from maternal use as part of the PREVENT pregnancy prevention programme.

The product information of all valproate-containing medicines is 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 the use of valproate in men. In addition, educational materials will be available for healthcare professionals.

These include:

- A new patient guide for men outlining information on the potential risk, which should be provided to male patients using valproate.
- An update of the existing patient card with information for male patients, which will be attached to the outer packaging of Epilim packs, so that it will be provided in the pharmacy to the patient each time the medicine is dispensed.
- The existing guide for healthcare professionals for valproate's PREVENT pregnancy prevention programme will be updated to include a dedicated section on the use of valproate in male patients.

Hard copies of the educational materials will be disseminated by the licensing holder in Ireland following approval by the HPRA. Copies will also be published on the HPRA's valproate special topics[8] page and can be found using the Find a medicine[9] search. It is anticipated that these materials will be available by June.

** Valproate product information and educational materials are available from the HPRA website (www.hpra.ie)*

References

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