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

Valproate-containing medicines▼ are sodium valproate [Epilim, Convulex , Episenta , Epival]; sodium valproate, valproic acid [Epilim Chrono/Chronosphere , Dyzantil]; valproate semisodium [Depakote, Syonell, Belvo].

2nd September 2024

Dear Healthcare Professional,

Sanofi, on behalf of the Marketing Authorisation Holders of the valproate-containing medicines▼ named above, in agreement with the Medicines and Healthcare products Regulatory Agency (MHRA) would like to inform you of the following updates to the product information for all valproate-containing medicines:

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, the new advice is proposed as a precautionary measure.**

New measures for valproate use in male patients

- **Male patients should be informed, by GPs and specialists, about the potential risk of NDDs and the need for male patients and their female partner to use effective contraception, while using valproate and for 3 months after stopping the treatment.**
- **For male patients planning to father a child, the specialist should consider and discuss other suitable treatment options with the patient. Individual circumstances should be evaluated for each patient.**
- **Male patients should be advised not to donate sperm during treatment or for at least 3 months after treatment discontinuation.**
- **Treatment with valproate in male patients should be regularly reviewed by GPs or specialists.**
- **This does not replace the existing requirement for two specialists to independently consider and document that there is no other effective or tolerated treatment or the risks are not applicable at initiation of treatment in male patients under 55 years.**
- **An updated patient guide should be provided to male patients using valproate - this is expected in Autumn 2024.**

An updated patient card should be given to male patients when valproate is dispensed - this is expected in Autumn 2024.

Background on the safety concern

The MHRA, with independent advice from the Commission on Human Medicines, has evaluated data from a study (EUPAS32401) 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 and the risk of major congenital malformations in offspring paternally exposed to valproate as monotherapy, compared to lamotrigine or levetiracetam as monotherapy treatment, in the 3 months period prior to conception. This retrospective observational study was conducted using data from multiple registry databases in Denmark, Sweden and Norway. No increased risk of major congenital malformations was reported. 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 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, which may lead to permanent disability. Children exposed in-utero have also a high risk of major congenital malformations (about 11%).

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 alongside the educational materials to inform healthcare professionals and patients of the potential risk of NDD in children of men treated with valproate in the 3 months before conception and to provide guidance regarding use of valproate in men. In addition, educational materials will be available for healthcare professionals and male patients in Autumn 2024. 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 updated patient card, which should be provided to both male and female patients when they are dispensed valproate.
- An updated risk acknowledgement form for males, to be used for new male patients starting a medicine containing valproate.

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle

You can report via:

- the Yellow Card website (https://yellowcard.mhra.gov.uk)
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

- Valproate▼ is subject to additional monitoring. This will allow quick identification of new safety information.
- Please report ANY suspected adverse drug reactions (ADRs) to new drugs and vaccines identified by the black triangle ▼ to the MHRA through the Yellow Card Scheme.

Yours faithfully,

Deborah Woods
Sanofi UK and Ireland Head of Medical, General Medicines