23 January 2024

Epilim® (Valproate): Updates and new measures relating to the risk of neurodevelopmental disorders in children of fathers treated with valproate

Dear Healthcare Professional,

Following further analysis of the results reported in our recent communication dated 20 March 2023, Sanofi-Aventis Singapore Pte Ltd would like to update you on the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception compared to those treated with lamotrigine / levetiracetam, as well as the new measures that will be introduced to address this risk.

Summary

- **A retrospective observational study (EUPAS34201)[1] on electronic medical records in 3 European Nordic countries indicated an increased risk of neurodevelopmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate in the 3 months prior to conception compared to those treated with lamotrigine or levetiracetam.**

- **The study results are as follows:**
  - **The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% (previously reported as 5.6% to 6.3%) in the valproate group versus between 2.3% to 3.2% (previously reported as 2.5% to 3.6%) in the composite lamotrigine/levetiracetam monotherapy group.**
  - **The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07) (previously reported as 1.47 (95% CI: 1.10, 1.96).**

- **Due to study limitations, it was not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributed to the overall increased risk of NDDs.**

- **As a precautionary measure, prescribers are advised to:**
  - **inform male patients of the potential risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception,**
  - **discuss alternative therapeutic options with the patients,**
  - **discuss with the patient, at least annually, on the need for effective contraception while using valproate and for 3 months after stopping the treatment,**
  - **inform the patient about the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or mania,**
  - **use and complete the Annual Risk Acknowledgement Form for male patients, and**
  - **provide them with the Patient Guide dedicated to male patients.**

The Singapore package insert for Epilim® has been amended to include the updated information on this risk, as well as the new measures that will be introduced. The updated educational materials will also be disseminated to healthcare professionals when available. For further information on the background to this safety update, please refer to the Annex.

Educational Materials

Healthcare professionals are encouraged to utilise the updated educational materials that have been developed to inform male patients on the potential risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception, as well as to provide guidance regarding use of valproate in men of reproductive potential. These educational materials consist of:

- A **Patient Guide for male patients**,
- An **Annual Risk Acknowledgment Form for male patients** to be used at treatment initiation and during annual review of valproate treatment in male patients by specialist prescribers,
- An **updated HCP Guide** to include new safety information related to the use of valproate in male patients, including details of the study results and clinical recommendations.

Call for reporting

HSA has been notified of this safety update. Healthcare professionals are encouraged to report any suspected adverse drug reactions to Sanofi Pharmacovigilance via email at PV.SIN@sanofi.com, or the Vigilance & Compliance Branch, Health Products Regulation Group, HSA at Tel: 6866 1111, or report online at https://www.hsa.gov.sg/adverse-events.

Company contact point

For medical inquiries or additional information, please email Sanofi at Med.SAMS@sanofi.com with the subject title "EPILIM".

Yours faithfully,

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Dr Shiva Patil
Medical Head TMS, Medical Foundation Community
Head Asia & Eurasia, Medical Foundation

Reference:

1. https://catalogues.ema.europa.eu/node/3611/administrative-details

Annex

Approved indications

Epilim® (valproate) is approved in Singapore for the following indications:

Oral

Epilepsy
For oral administration in the treatment of generalised, partial or other epilepsy with the following patterns of seizures:

- absence
- myoclonic
- tonic-clonic
- atonic
- mixed
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As well as, for partial epilepsy:

- simple or complex seizures
- secondary generalised seizures
- specific syndromes (West, Lennox-Gastaut)

Mania
For treatment of mania where other therapy has proved inadequate or is inappropriate.

Injectable

The treatment of epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

In the treatment of generalised or partial epilepsy, particularly with the following patterns of seizures:

- absence
- myoclonic
- tonic-clonic
- atonic
- mixed

As well as, for partial epilepsy:

- simple or complex seizures
- secondary generalised seizures
- specific syndromes (West, Lennox-Gastaut)

Background on the safety concern

In 2018, the European Medicines Agency (EMA) requested that pharmaceutical companies marketing valproate-containing medicines, or one of its derivatives, conduct a study with the primary objective of evaluating the association between paternal exposure to valproate and the risk of neurodevelopmental disorders (NDDs) in their offspring, in comparison to lamotrigine / levetiracetam.

The retrospective observational study was conducted using data from multiple registry databases in Denmark, Sweden and Norway. A cohort of offspring paternally exposed to valproate was compared to a cohort of offspring paternally exposed to lamotrigine / levetiracetam. The primary outcome of interest was NDDs (composite endpoint including autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorder, movement disorder) in offspring up to 12 years of age.

In our earlier communication dated 20 March 2023, healthcare professionals were informed about the study results from the meta-analysis. Due to a discovery of quality issues within the study datasets, a re-evaluation of the updated data was conducted following rectification of the issues.

The revised meta-analysis found that:

- The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine / levetiracetam monotherapy group. The pooled adjusted HR for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07).

- Due to the study limitations, it was not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributed to the overall increased risk of NDDs.

Despite the study limitations, as a precautionary measure, prescribers are advised to inform male patients of this potential risk and to discuss with the patient the need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment. There is currently no data on the risk to children fathered more than 3 months after stopping valproate treatment (i.e., allowing a new spermatogenesis without valproate exposure).

Prescribers are also advised to counsel male patients:

- not to donate sperm during treatment and for 3 months after stopping treatment,
- to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child and before discontinuing contraception,
- that he and his female partner should contact their doctor for counselling in case of pregnancy if he used valproate within 3 months prior to conception.