20 March 2023

Epilim® (Valproate) - Risk of neurodevelopmental disorders including autism spectrum disorders in children after paternal exposure

Dear Healthcare Professional,

Sanofi-Aventis Singapore Pte Ltd would like to inform you of new safety updates regarding a higher risk of neurodevelopmental disorders (NDDs), including autism spectrum disorders, in children after paternal exposure to valproate as compared to lamotrigine/levetiracetam.

Key information

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

- **The adjusted cumulative risk of NDDs ranged between 5.6% to 6.3% in the valproate group versus between 2.5% to 3.6% in the composite lamotrigine/levetiracetam monotherapy exposure. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 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. Further investigations are needed.**

- **Prescribers are advised to inform male patients of this potential risk and consider alternative therapeutic options with the patients. In men initiating or remaining on valproate treatment, it is recommended for prescribers to discuss with the patient, at least annually, the need for effective contraception, and to ensure that the male patient has acknowledged the risk and precautions associated with valproate use.**

The Singapore package insert for Epilim® is being revised to reflect results from the retrospective observational study and highlight the increased risk of NDDs in children of fathers treated with valproate at the time of conception. For further information on the background to this safety update, please refer to the Annex.

Educational Materials

Revised and new educational materials have been developed by Sanofi-Aventis Singapore Pte Ltd to inform healthcare professionals (HCPs) and patients of new safety information and guidance regarding the use of

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MAT-SG-2300029-1.0 02/2023

valproate in men of reproductive potential:

- 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.
- a new **Patient Guide for male patients** for distribution to all male patients of reproductive potential using valproate.
- a new **Annual Risk Acknowledgement Form (ARAF) for male patients** to be used at the time of treatment initiation and during each annual review of valproate treatment by the specialist.

These educational materials will be disseminated to HCPs upon the Health Sciences Authority's (HSA) approval of the revised package insert.

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,

Lokesh BN (Feb 17, 2023 12:39 GMT+8)

Dr Lokesh B N
TMS EP Medical Lead

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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

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

The new safety information regarding the risk of NDDs, including autism spectrum disorders (ASD), in children after paternal exposure to valproate arose from a retrospective observational study on electronic medical records in 3 European Nordic countries. This study was a post-authorisation safety study (PASS) requested by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) to evaluate the association between paternal exposure to valproate and the risk of NDDs, including ASD, as well as congenital abnormalities in offspring.

The study indicated that there was an increased risk of NDDs in children born to men treated with valproate at time of conception compared to those treated with lamotrigine or levetiracetam, as detailed below:

- The adjusted cumulative risk of NDDs ranged between 5.6% to 6.3% in the valproate group versus between 2.5% to 3.6% in the composite lamotrigine/levetiracetam monotherapy exposure. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.47 (95% CI: 1.10, 1.96).

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

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