19 May 2023

Valproate: Potential risk to children of fathers treated with valproate - New information regarding risk of neurodevelopmental disorders including autism spectrum disorders after paternal exposure to valproate in comparison to lamotrigine/levetiracetam

Dear Healthcare Professional,

This letter is sent in agreement with Medsafe to inform you of new warnings and measures to inform about higher risk of neurodevelopmental disorders (NDD) 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 indicates an increased risk of NDDs in children (from 0 to 11 years old) born to men treated with valproate at 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 is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. Further investigations are needed.**

- **As a precautionary measure, the prescriber should inform the male patients of this potential risk and consider alternative therapeutic options with the patients. In men initiating or remaining on valproate treatment, the need for effective contraception should be discussed with the patient, at least annually. The prescriber should ensure the male patient has acknowledged the risk and precautions associated with valproate use.**

SUMMARY OF CHANGES TO THE DATA SHEET

Section Changed	Summary of New Information
4.4	To add risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD) after paternal exposure to valproate
4.6	To add risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD) after paternal exposure to valproate
5.3	To amend nonclinical testicular findings.

EDUCATIONAL MATERIALS

Revised or new Educational Materials have been developed in order to inform HCPs and patients on the warnings and provide guidance regarding use of valproate in men of reproductive potential:

- the HCP Guide is updated to include information for male patients. It contains details of the study results and clinical recommendations and should be read carefully.
- A male Patient Guide is created. A copy of this patient guide should be provided to all male patients of reproductive potential using valproate.
- Copies of these materials are accessible via: www.sanofi.com.au/valproate or the QR code on the carton.

CALL FOR REPORTING

Please remember that any suspected adverse events should be reported to Medsafe.

COMPANY CONTACT

Adverse reactions can also be reported directly to Sanofi: email ae@sanofi.com or phone 0800 283 684.
Our medical information department can be contacted for further information at medinfo.australia@sanofi.com or 0800 283 684.

Please review the full product before prescribing:

Epilim: ***https://www.medsafe.govt.nz/profs/Datasheet/e/Epilimtabsyrliqiv.pdf***

Epilim IV: ***https://www.medsafe.govt.nz/profs/Datasheet/e/EpilimIV.pdf***

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Yours faithfully,

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