28 November 2023

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

Dear Healthcare Professional,

In agreement with Medsafe, a letter was distributed in May 2023 to inform you of new warnings and measures relating to potential the higher risk of neurodevelopmental disorders (NDD) including autism spectrum disorders in children after paternal exposure to valproate as compared to lamotrigine/levetiracetam. Subsequently, a reanalysis was undertaken to address some data discrepancies which have now been corrected.

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 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% 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 1.50 (95% CI: 1.09-2.07)**

- **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.**

- **Despite the study limitations, by way of precaution, the prescriber should:**
  - **inform male patients of this potential risk,**
  - **discuss alternative therapeutic options with the patients,**
  - **discuss at least annually the need for effective contraception while using valproate and for 3 months after stopping the treatment,**
  - **Inform male patients to avoid donating sperm while using valproate and for 3 months after stopping the treatment,**
  - **Inform patients of the potential risks to children fathered more than 3 months after stopping valproate are unknown,**
  - **inform the patient about the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorders,**
  - **advise patients of the new patient guide dedicated to male patients.**

- **The product information and educational materials for valproate-containing medicines have been updated to acknowledge the risk and advise of the precautions required.**

SUMMARY OF CHANGES TO THE DATA SHEET

Section Changed	Summary of New Information
4.4	To amend risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD) after paternal exposure to valproate
4.6	To amend risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD) after paternal exposure to valproate
4.8	To add Pelger-Huet anomaly

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 has been updated to include information regarding male patients. It contains details of the study results and clinical recommendations and should be read carefully.
- A male Patient Guide has been created. All male patients of reproductive potential using valproate should be made aware of this guide.
- 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 Data Sheet 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,

James Scott
Head of Medical – General Medicines ANZ