NSW Health

Potential risk of neurodevelopmental disorders in children of fathers treated with valproate

SAFETY INFORMATION 007/24

Issue date:	11 November 2024
Content reviewed by:	Medication Safety Expert Advisory Committee.
Distributed to:	Chief Executives, Directors of Clinical Governance, and the Director, Regulation and Compliance Unit.
KEY MESSAGE:	Inform clinicians of new warnings regarding a higher risk of neurodevelopmental disorders, including autism spectrum disorders, in children born to men treated with valproate during the time of conception compared to lamotrigine or levetiracetam.
ACTION REQUIRED BY:	Chief Executives, Directors of Clinical Governance.
REQUIRED ACTION:	1. Distribute this Safety Information to all relevant clinicians and clinical departments where valproate is dispensed, prescribed or administered. 2. Continue to report any incidents and adverse effects associated with valproate into the local incident management system (e.g., ims⁺) and to the TGA.
DEADLINE:	N/A
We recommend you also inform:	Directors, Managers and Staff of: • Medical Services • Pharmacy Departments • Nursing/Midwifery Services • Women's Health, Gynaecology and Obstetrics Services • Neurology • Psychiatry and Mental Health Drug and Therapeutics Committees All other relevant clinicians, departments and committees.
Website:	https://www.health.nsw.gov.au/sabs/Pages/default.aspx http://internal.health.nsw.gov.au/quality/sabs/index.html
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Contact: Clinical Excellence Commission
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Situation

The Product Information (PI) for various brands of valproate have been updated to include precautionary information about the increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate during the time of conception.

Sanofi, the Australian sponsor of the originator brand of valproate, has issued a Dear Healthcare Professional letter to notify clinicians about these new warnings and has also released new and revised educational materials for both clinicians and patients. These materials aim to educate on the precautions and offer guidance regarding the use of valproate in men of reproductive potential.

The Therapeutic Goods Administration (TGA) is currently reviewing the use of valproate in both women and men of reproductive potential, and additional information may be published by the TGA based on the findings of this review.

Background

Valproate is commonly used to treat epilepsy and bipolar disorder. Valproate is a known teratogen and there is already advice surrounding the use of this medicine in girls and women of childbearing potential.

A retrospective observational study on electronic medical records in three European Nordic countries has indicated an increased risk of NDDs in children (aged 0 to 11 years) born to men treated with valproate in the 3 months before conception compared with those treated with lamotrigine or levetiracetam. The pooled adjusted hazard ratio was 1.47 (95% CI: 1.10, 1.96).

Assessment

It is necessary to inform patients and healthcare professionals about the potential risk of NDDs in children of fathers treated with valproate.

The Product Information (PI) has been updated in multiple sections to include the risk of NDDs following paternal exposure to valproate. Refer to **Table 1** for a summary of the changes to the PI for valproate.

Table 1. Summary of changes to the PI for valproate

Section changed	Summary of new information
4.4, 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.

The precautions regarding the increased risk of NDDs in children of fathers treated with valproate have also been included in the Australian Medicines Handbook (AMH) monograph for valproate.

Sanofi has published materials for clinicians and patients about the warnings regarding valproate use in men of reproductive potential, as well as providing guidance to support informed decision-making. These materials can be accessed via the Sanofi website or by scanning the QR code on the packaging. These materials include:

- Healthcare Professionals Valproate Guide (updated to include information for male patients).
- Male Patient Guide (new).

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Recommendations

It is important that clinicians involved in the prescribing, dispensing, and administration of valproate are aware of the risks associated with its use in men of reproductive potential. Recommended strategies include:

- Ensuring valproate therapy is overseen by a specialist prescriber (neurologist or psychiatrist) where the benefits and risks can be considered. This is particularly relevant for male patients commenced on valproate during hospital admission and should be addressed during transitions of care (for example, including this information in the discharge summary).
- Ensuring shared decision-making with male patients prior to commencing valproate and providing comprehensive information about potential risks, benefits, and alternative treatment options.
- Discussing with male patients, the importance of effective contraception, including for their female partner, during treatment and for 3 months after stopping treatment. This conversation should occur at least annually.
- Informing male patients to avoid donating sperm during treatment and for at least 3 months after stopping treatment with valproate.
- Informing patients that the potential risks to children conceived **more** than 3 months after stopping valproate are not known at this stage. 3 months is the time required for new spermatogenesis (production of sperm) without valproate exposure.
- Ensuring regular medication review for male patients prescribed valproate to assess its ongoing suitability, particularly before stopping contraception and when the patient is planning to conceive a child. Seek advice from the Mental Health or Neurology team for further guidance.
- Ensuring all male patients of reproductive potential prescribed valproate receive the Male Patient Guide developed by Sanofi, and ensuring they are equipped with essential information about potential risks when planning to conceive and their responsibilities regarding effective contraception.
- Documenting the outcomes of any discussions and decisions, including the need for valproate treatment and contraception plans in the patient's medical record.
- Ensuring initial and ongoing education to clinicians about the risks associated with valproate use in both male and female patients of reproductive potential. The Healthcare Professionals Valproate Guide for management of girls, women of childbearing potential, and men treated with valproate should be read carefully before prescribing valproate.
- Reporting any suspected adverse events related to valproate use in the local incident management system (e.g., ims⁺) and to the TGA. Adverse reactions should also be reported directly to Sanofi at ae@sanofi.com or phone 02 8666 2123.

Further information

Statement from the Royal Australian and New Zealand College of Psychiatrists

Valproate use in men: as a precaution, men and their partners should use effective contraception – Medicines and Healthcare Products Regulatory Agency

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