



An update on valproate

A publication by the National Medicines Information Centre (NMIC)

Risks associated with valproate use Current risk management advice Advice for Healthcare Professionals
Educational Materials Useful Resources

Key Facts:

- There are known teratogenic and neurodevelopmental risks associated with the maternal use of valproate
- HPRA pharmacovigilance updates highlight the safety concerns, restrictions and contraindications associated with the prescribing and use of valproate in girls and women of childbearing potential
- Due to the potential increased risk of neurodevelopmental disorders in children born to men treated with valproate during the three months before conception, the EMA has also recommended precautionary measures for male patients
- HPRA valproate risk minimisation measures are tailored to the specific responsibilities and roles of each Health Care Professional (HCP)

Background

Valproate medicines have been in use in EU countries since 1967.¹ In Ireland, valproate is currently approved, under the brand name Epilim®, for treatment of epilepsy and for treatment of mania in bipolar disorder (when lithium is contraindicated or not tolerated).² In some cases, **valproate may be the only treatment option for patients (when other treatments are ineffective or not tolerated)** to maintain good seizure control and to reduce the risk of injuries from seizures and reduce mortality due to epilepsy.

Valproate carries a known risk of birth defects when taken during pregnancy.² Recent figures from the UK show that valproate was prescribed to 247 patients in England during their pregnancy between April 2018 and September 2021.³

In Ireland, HSE Primary Care Reimbursement Service (PCRS) data indicate that in 2023, there were over 20,435 patients in receipt of valproate on the Community Drug Schemes (CDS); with women aged between 16 and 44 accounting for 1,251 patients.⁴ It should be noted that these figures represent the total number of patients across all CDS and therefore may contain some double counting, where patients with a dispensing claim on multiple schemes would be counted twice.

Following two EU-wide safety reviews of valproate in 2014 and 2018,^{5,6} the Irish regulatory body, the Health Products Regulatory Authority (HPRA) issued several communications to healthcare professionals, recommending risk minimisation measures for the use of valproate in **girls and women of childbearing potential**.⁷⁻¹⁰

The UK regulatory authority, the Medicines and Healthcare products Regulatory Agency (MHRA) has issued similar recommendations.¹¹

In Europe, the effectiveness of these risk minimisation measures is monitored via the European Medicines Agency's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC).

In August 2023, PRAC published an assessment report which included a review of preliminary data from an effectiveness study¹² and recommended changes to educational materials to (1) address preliminary findings and to (2) provide greater clarity on the roles of different HCPs as part of multidisciplinary care model for patients treated with Epilim®.¹²

These recommendations have been incorporated into updated educational materials provided by the HPRA in Ireland.¹³⁻¹⁵

In September 2023, a Direct Healthcare Professional Communication (DHPC) was issued by Sanofi® (the Marketing Authorisation Holder (MAH)), and approved by HPRA, communicating an ongoing review into the risks associated with the use of valproate.¹⁶ This was further supported by the HPRA's Drug Safety Newsletter in November 2023.²⁰

More recently (January 2024) PRAC recommended precautionary measures for valproate use in **male patients**.²¹ These precautionary measures were issued to address a **potential increased risk of neurodevelopmental disorders** in children born to men treated with valproate during the three months before conception.²¹

The new precautionary measures for valproate use in male patients were then communicated to Irish healthcare professionals via the MAH in a HPRA approved DHPC in February 2024,²² and again this was further supported by a Drug Safety Newsletter in April 2024.²³

RISKS ASSOCIATED WITH VALPROATE USE

In Females - Teratogenic risk

In females, both valproate monotherapy and valproate polytherapy including other antiepileptics, are frequently associated with abnormal pregnancy outcomes.² Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate.²



It is estimated that approximately 11% of children exposed to valproate in utero have **major congenital malformations** at birth.^{2,3,5-11,13,14} This risk is greater than in the general population (about 2-3%).^{2,13}

The most common types of malformations include: neural tube defects, face and skull malformations e.g., 'cleft lip' and 'cleft palate', hearing impairment or deafness as well as malformations of the limbs, heart, kidney, urinary tract, sexual organs and of the eyes that may affect vision.^{2,24}

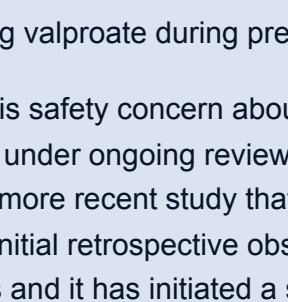
Available evidence does not show that folate supplementation prevents birth defects due to valproate exposure.¹³

Although structural malformations can be the most obvious adverse pregnancy outcome, it is known that up to 30 - 40% of children exposed to valproate in utero may experience delays in their early development i.e., **neurodevelopmental disorders (NDDs)**.^{2,13} This can present as infants being late in learning to walk and talk, poorer speech and language skills and having a lower IQ than other children of the same age.^{2,13}

Children exposed to valproate in utero may be more likely (approximately 1.5-fold) to develop attention deficit hyperactivity disorder (ADHD) compared to the unexposed population.^{5,13} Childhood autism is approximately 5 times more likely compared with unexposed children.^{2,5,13}

In Men - Paternal exposure

Following a previous EU-wide review of valproate use during pregnancy, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) evaluated data from a study (EUPAS34201) conducted by pharmaceutical companies of valproate containing products.^{22,23,25}



This retrospective observational study was conducted using secondary data from multiple registry databases in Denmark, Sweden and Norway.^{22,25} The primary objective was to investigate the risk of NDDs in offspring paternally exposed to valproate as monotherapy, compared to lamotrigine or levetiracetam as monotherapy treatment, in the 3-month period prior to conception.^{22,25}

The study also did not evaluate the risk of NDDs to children born to men who had discontinued valproate treatment for more than 3 months before conception (i.e., allowing a new spermatogenesis without valproate exposure).^{19,22}

Due to these study limitations, the risk of NDDs in children of fathers that used valproate in the 3 months prior to conception is considered a **potential risk** and a causal association with valproate is not confirmed.²² However, the **EMA has recommended precautionary measures for valproate use by male patients**.^{21-23,26}

The meta-analysis of the three cohorts found a statistically significant increased risk of NDDs, with paternal exposure to valproate in the 3 months prior to conception, when compared to lamotrigine/levetiracetam monotherapy group.^{22,25,26}

It should be noted that the potential risk associated with valproate use in men, is much lower than the estimated 30-40% risk of neurodevelopmental disorders in children born to mothers taking valproate during pregnancy.^{22,27}

The adjusted cumulative risk of NDDs ranged from 4.0% to 5.6% in the valproate treated group versus 2.3% to 3.2% in the composite lamotrigine/levetiracetam treated group. The pooled adjusted hazard ratio was 1.50 (95% CI: 1.09 to 2.07).^{22,25,26}

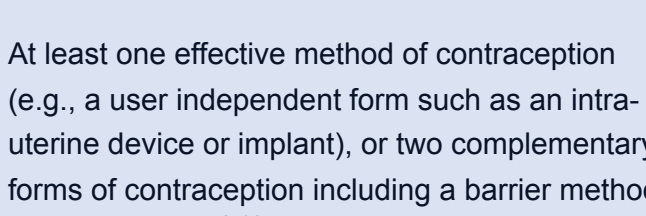
Of interest, this safety concern about valproate use in men is under ongoing review.²⁸ PRAC has highlighted a more recent study that does not replicate the initial retrospective observational study findings and it has initiated a signal procedure to understand the difference in the findings across the studies.²⁸

Therefore, around 5 children in every 100 had NDDs when born to fathers treated with valproate compared to around 3 children in every 100 when born to fathers treated with lamotrigine or levetiracetam.¹⁵

The study was not large enough to investigate associations with specific NDD subtypes and did have a number of limitations including: potential confounding by indication, differences in follow-up time between exposure group and the background risk was not established as an untreated group was not included as part of the study.^{13,22}

RECENT PHARMOVIGILANCE UPDATES & CURRENT RISK MANAGEMENT ADVICE

As part of the pharmacovigilance process, there have been several updates reflecting the most recent valproate safety concerns.



PREVENT Programme

In 2014 and 2018 a number of steps were taken to better inform women about the risks of valproate use and discourage use of valproate in girls and women unless there was no alternative.^{1,5,8-10} More recently (2024-2025) strengthened warnings and risk minimisation measures to prevent valproate exposure during pregnancy have been brought into effect.^{11,13,14,21-23,27,29}

When treatment is considered necessary, valproate must be prescribed and dispensed according to the Valproate Pregnancy Prevention Programme, which in Ireland is known as PREVENT.

The PREVENT programme has been implemented nationally and across the EU since 2018.¹⁰ As part of PREVENT, valproate medicines are contraindicated i.e., must not be used, in girls and women able to have children unless the terms of a special valproate pregnancy prevention programme known as PREVENT are followed.

Of note there are differences between the two indications (epilepsy and bipolar disorder) regarding **use in pregnancy**.

1. In epilepsy, valproate is contraindicated unless there is no suitable alternative treatment.
2. In bipolar disorder, valproate is contraindicated.

Learn more

Additional key elements of the PREVENT programme (full details can be found via the HPRA website) include recommendations from the EMA.^{8,10} as follows:

• Pregnancy test

Pregnancy must be excluded before treatment with valproate commences. A negative pregnancy test result in women of childbearing potential, confirmed by a healthcare provider, is required to rule out unintended use in pregnancy.^{2,13,14}

• **Pregnancy planning**

If a woman being treated with valproate for either epilepsy or bipolar disorder is planning a pregnancy, then a specialist should be consulted prior to conception.^{2,13}

If a woman being treated with valproate for **epilepsy** is planning a pregnancy, then a specialist must reassess the need for valproate and **consider alternative therapies**. Every effort should be made to switch the patient to another treatment prior to conception and before contraception is discontinued.^{2,13}

If a woman is being treated with valproate for **bipolar disorder** the specialist should be consulted prior to conception so that treatment with valproate can be discontinued; an alternative treatment can then be commenced before contraception is discontinued.^{2,13}

• Contraception

Women of childbearing potential taking valproate must use effective contraception without interruption for the entire duration of treatment with valproate.²

• Annual treatment reviews

The specialist should review the patient at least annually and decide whether valproate remains the most suitable treatment for the patient. An annual risk acknowledgement form is used to help ensure that patients know and understand the risks related to the use of valproate during pregnancy and the need to avoid becoming pregnant while taking valproate.¹⁰

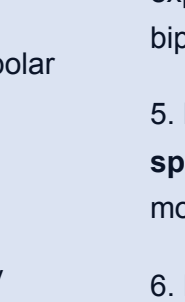
At least one effective method of contraception (e.g., a user independent form such as an intra-uterine device or implant), or two complementary forms of contraception including a barrier method should be used.^{2,13}

The specialist should discuss the annual risk acknowledgement form at initiation and during each annual review with the patient, and should ensure that the patient has understood its content.^{2,13,14}

Individual circumstances should be evaluated in each case and the patient should be fully involved in the discussion regarding the method of contraception chosen, to guarantee her engagement and compliance with the chosen measures. The patient should be referred for contraceptive advice if not using effective contraception currently.¹⁴

A copy of the signed risk acknowledgement form should be filed in the patient's medical record and a copy should be provided to both the patient and her GP.¹⁶

Of note, oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy.⁹ Bear the possibility of this interaction in mind.³⁰



• In case of pregnancy

If a woman using valproate becomes pregnant or thinks that she is pregnant she should not stop taking valproate. It is important that she immediately seek urgent review and be seen by a specialist to re-evaluate her treatment with valproate and to consider alternative treatment options.^{2,13,14}

These recommendations also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.²

In **epilepsy**, maternal tonic-clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and baby. If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, **in exceptional circumstances** a pregnant woman must receive valproate for **epilepsy**, it is recommended to use the lowest effective dose and divide the daily dose into at least two single doses. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.^{14,13}

Regularly review treatment in male patients to evaluate whether valproate remains the most suitable treatment for the patient.

Patients (and their partners) with a valproate exposed pregnancy should be referred to an appropriate specialist for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects and other physical malformations.¹³

For male patients planning to conceive a child, suitable alternative treatment options should be considered and discussed with the patient. It is recommended that advice from a specialist experienced in the management of epilepsy or bipolar disorder should be sought as appropriate.

Although folate supplementation before the pregnancy may reduce the risk of neural tube defects which may occur in all pregnancies, available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.¹³

Male patients should be advised **not to donate sperm** during treatment and for at least three months after treatment discontinuation.

According to the Summary of Product Characteristics (SmPC)² and the guide for healthcare professionals¹³, as a precautionary measure, it is recommended that prescribers¹³:

6. Provide patients with the HPRA-approved **patient guide**.

1. Inform male patients about the potential risk of NDDs in children born to men treated with valproate in the 3 months prior to conception.
2. Discuss regularly the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after stopping the treatment.

7. Regularly review treatment in male patients to evaluate whether valproate remains the most suitable treatment for the patient.

Similarly, the HPRA approved further guidance (2024) to inform healthcare professionals regarding the potential risk of NDDs in children of fathers treated with valproate in the three months before conception.¹³

8. Male patients should be advised **not to donate sperm** during treatment and for at least three months after treatment discontinuation.

Risk minimisation measures for men

9. Provide patients with the HPRA-approved **patient guide**.

In **epilepsy** is contraindicated in pregnancy **unless** there is no suitable alternative treatment.

10. Prescribers should discuss the risk with their patients and ensure that patients **understand** the conditions associated with the PREVENT programme. Patients should also receive and understand the **patient guide**.

• valproate is contraindicated in women of childbearing potential, unless all the conditions of the pregnancy prevention programme PREVENT are met.

These recommendations also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.²

In **bipolar disorder**

11. Prescribers should discuss the risk with their patients and ensure that patients **understand** the conditions associated with the PREVENT programme. Patients should also receive and understand the **patient guide**.

• valproate is contraindicated in pregnancy.

12. Prescribers should discuss the risk with their patients and ensure that patients **understand** the conditions associated with the PREVENT programme. Patients should also receive and understand the **patient guide**.

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Similarly, the HPRA approved further guidance (2024) to inform healthcare professionals regarding the potential risk of NDDs in children of fathers treated with valproate in the three months before conception.¹³

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16. Provide patients with the HPRA-approved **patient guide**.

2. Discuss regularly the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after stopping the treatment.

17. Regularly review treatment in male patients to evaluate whether valproate remains the most suitable treatment for the patient.

Further to the guidance documents available for patients,^{14,15} a **patient card** should be attached to the packaging of valproate products to facilitate discussions about the risks associated with valproate use between the pharmacist and the patient each time valproate is dispensed.¹⁷ Pharmacists are reminded to confirm if the patient has received a copy of the patient guide, to provide one if necessary and to remind patients of the need for annual specialist review.

2. Changes to dispensing practices:

Valproate containing medicines should only be dispensed in their original packaging whenever possible to:

- ensure that all patients receive a **package leaflet**
- ensure that all appropriate safety information is visible
- to prevent broken bulk dispensing^{13,18}

When broken bulk dispensing cannot be avoided, a copy of the package leaflet should always be provided with a warning sticker added.³²

The pack size of valproate containing medicines (Epilim®) has been reduced to mitigate against the need for broken bulk dispensing at the pharmacy level and to ensure that all patients receive a package leaflet and the outer carton (which displays visual warnings) along with the patient card at each dispensing.³²

A best-practice location for the dispensing label has been identified on the outer package.³¹ This is to ensure that the information warnings contained elsewhere on the outer packaging are not concealed by a dispensing label.²⁹

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