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An update on valproate

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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 study[12] 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.[13-18]

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.[19] 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]

This bulletin aims to discuss the risks associated with valproate use, to outline the recent HPRA pharmacovigilance updates and to highlight the risk minimisation materials available to guide safe prescribing practices.

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 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]

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]

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]

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).[13,22]

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]

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]

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]

RECENT PHARMCOVIGILANCE UPDATES & CURRENT RISK MANAGEMENT ADVICE

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

prevent
valproate pregnancy prevention programme

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.[5,6,8,10] 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]

In female children and women of childbearing potential, valproate (Epilim®) **must be** initiated and supervised by a **specialist** experienced in the management of epilepsy or bipolar disorder.

Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

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]

• Contraception

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

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]

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]

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.[2] Bear the possibility of this interaction in mind.[30]

• 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]

• 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.[16]

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]

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]

• 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]

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.[7,8,13]

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]

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]

ADVICE FOR HEALTHCARE PROFESSIONALS

To complement the PREVENT programme, the HPRA has approved a guide for healthcare professionals who manage girls and women of childbearing potential treated with valproate.[13] The following risk minimisation measures are recommended[13]:

Risk minimisation measures for women

1. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated. **In pregnancy** and in women of childbearing potential, new contraindications apply:

In epilepsy

♦ valproate is contraindicated in pregnancy **unless** there is no suitable alternative treatment.

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

In bipolar disorder

♦ valproate is contraindicated in pregnancy.

♦ valproate is contraindicated in women of childbearing potential, unless all the conditions of PREVENT are met.

2. In female children and women of childbearing potential valproate **must be initiated and supervised by a specialist** experienced in the management of epilepsy or bipolar disorder.

3. Healthcare professionals should prescribe and dispense valproate according to the PREVENT programme.

4. For women of childbearing potential who are currently using valproate, specialists should regularly re-evaluate treatment to ensure that the conditions of the pregnancy prevention programme are met and that valproate remains the most appropriate therapeutic option for them.

5. 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.

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]

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]

Risk minimisation measures for men

In male patients, it is recommended that valproate is initiated and supervised by a specialist experienced in the treatment of epilepsy or bipolar disorder, as appropriate.[2]

According to the Summary of Product Characteristics (SmPC)[2] and the guide for healthcare professionals[13], as a precautionary measure, it is recommended that prescribers[13]:

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.

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

4. 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.

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

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

Advice for Patients

Comprehensive patient guides are available via the HPRA website to ensure that both female and male patients who are taking valproate are fully aware of its teratogenic and neurodevelopmental risks and the recommended safety precautions required to minimise these risks associated with the use of valproate.[14,15]

Monitoring ▼

- In the European Union (EU), medicines that are being monitored particularly closely by regulatory authorities are labelled with a black inverted triangle (▼) in the product information.[31] Additional monitoring aims to **enhance reporting of suspected adverse drug reactions.**[31]
- Valproate is subject to this additional monitoring (▼) which will allow for the continued monitoring of the benefit/risk balance.[2]
- Healthcare professionals are reminded to report any pregnancy exposures and any associated suspected adverse reactions via the HPRA's online reporting service.[2]

Learn more about HPRA reporting

EDUCATIONAL MATERIALS TO GUIDE PRESCRIBING PRACTICES

While the approved product information i.e., the SmPC, package leaflet (PIL) and package labelling provide all the relevant valproate information, a number of recently updated educational materials are also available **to provide clear information** on specific risks and describe concisely what actions are required to prevent and minimise such risks.[13-18]

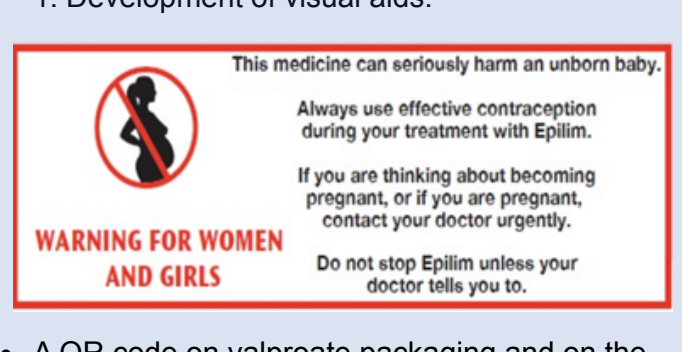
For Healthcare Professionals

Information on the safe prescribing of valproate for various healthcare professionals including **specialist prescribers, GPs, gynaecologists/obstetricians and midwives** is detailed in specific sections of the aforementioned HPRA's guide for healthcare professionals.[13]

The guide also outlines information for the **safe supply and counselling** of both girls and women of childbearing potential and of male patients treated with valproate.

Additional risk minimisation measures to further support **pharmacists** in the safe dispensing of valproate to patients include:

1. Development of visual aids:



- A QR code on valproate packaging and on the enclosed patient information leaflet links to the patient guide[13]
- A pregnancy warning symbol is now visible on the packaging[32]
- Poster material for display in pharmacies highlights risks and important actions[18]

2. Changes to dispensing practices:

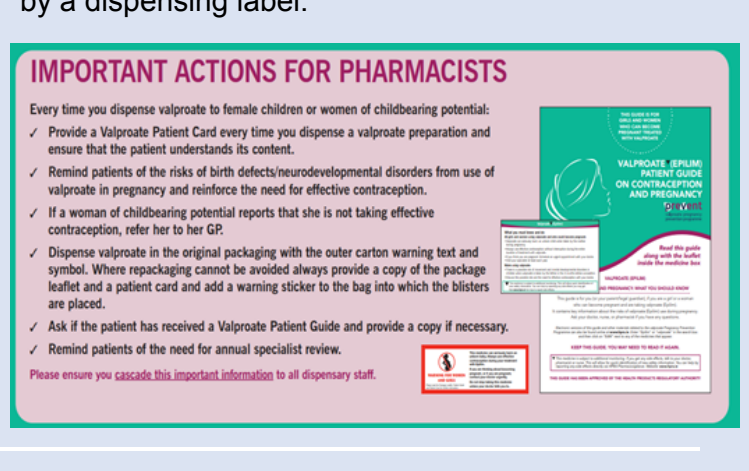
Valproate containing medicines should only be dispensed in their original packaging whenever possible to:

- 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 packaging. This is to ensure that the information warnings contained elsewhere on the outer packaging are not concealed by a dispensing label.[29]



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.

USEFUL RESOURCES

- Summary of Product Characteristics (SmPC), licenced product information. Available at hpra.ie and www.medicines.ie
- Health Products Regulatory Authority (HPRA) Precautionary measures for male patients using valproate-containing medicines
- HPRA Use of valproate-containing medicines by girls and women who can become pregnant
- HPRA Valproate guide for healthcare professionals (July 2024)
- HSE National Clinical Programme: Valproate Pregnancy Prevention Programme (PREVENT)
- National Institute for Health and Care Excellence (NICE). NICE Guideline: Epilepsies in children, young people and adults [NG217] (January 2025)
- College of Sexual and Reproductive Healthcare (CoSRH) [previously the Faculty of Sexual and Reproductive Healthcare (FSRH)]. FSRH statement: Paternal exposure to valproate and the risk of neurodevelopmental disorders in children (September 2024)
- Epilepsy Ireland
- European Medicines Agency (EMA)
- Organisation Anticonvulsant Syndromes Ireland (OACS)
- Best Use of Medicines in Pregnancy (BUMPS)

Summary:

- There are known teratogenic and neurodevelopmental risks associated with the parental use of valproate.
- The EMA, via its risk assessment committee PRAC, continues to provide pharmacovigilance updates highlighting safety concerns with the use of valproate in girls and women of childbearing potential.
- More recently, the EMA has recommended precautionary measures for the treatment of male patients; this is due to the potential increased risk of NDDs in children born to men treated with valproate during the three months before conception.
- The HPRA has approved updated guidance to reflect this information and as a result, a number of important tools are available to help guide the safe prescribing and supply of valproate to girls and women of childbearing potential and also to males who are treated with valproate.
- Not only do these educational materials support healthcare professionals in the safe and effective prescribing of valproate, the materials can be used to help ensure patients are fully informed of the risks of use and are better able to discuss options with their care providers.

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Our full list of references can be accessed via the *Reference List* button.

Reference List

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Feedback

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