Valproate and the PREVENT Programme

Elisabeth Doran
Clinical lead PREVENT Programme

Overview

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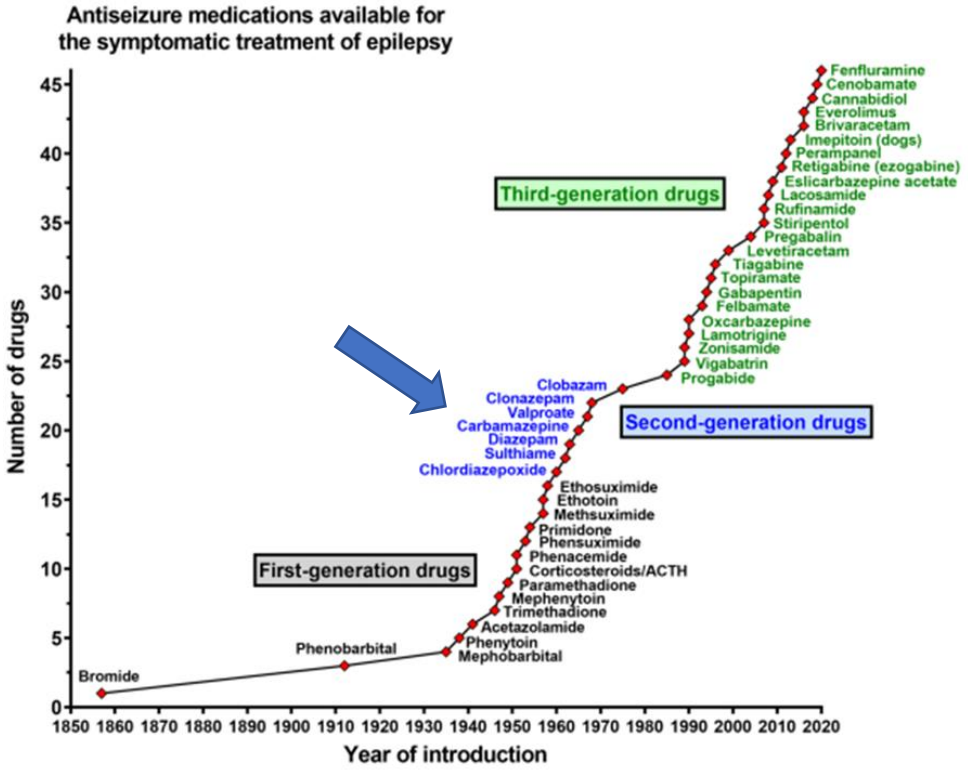
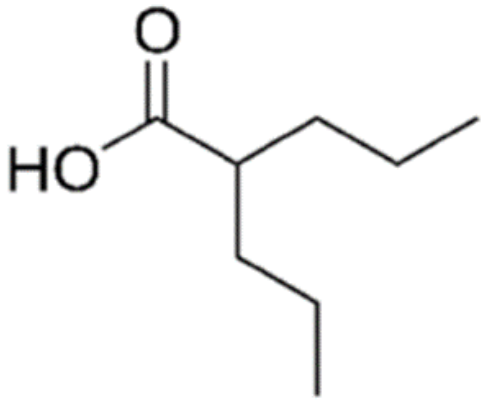
Valproate

- First derived from the valerian root in the 19th century
- Valproate was first licenced in Ireland in 1975
- It is used to treat epileptic seizures and affective disorder
- For generalized seizures, the efficacy and tolerability of valproate compares favourably to those of newer anti-epileptics
- Valproate remains one of the most commonly prescribed antiepileptic drugs worldwide



Valproate

- Valproic acid is a short-chain branched fatty acid
- Most formulations are salts e.g. Sodium Valproate
- The mechanism of action is not fully understood
- It acts as a Sodium channel blocker and NMDA-Receptor Channel blocker
- Modulates GABA transmission via its ability to inhibit GABA transaminase activity
- Together, these mechanisms are postulated to promote a net calming effect on brain activity



Valproic acid

Valproate - Teratogenicity

- Increased risk of foetal malformations was first reported in the 1980s
- 2013 data first emerged that showed that Valproate exposure in utero also causes development disorders
- Due to these findings the European Medicines Agency Pharmacovigilance Risk Assessment Committee strengthened restrictions on use of Valproate in girls and women in 2014
- In February 2018, the European Medicines Agency recommended further enhanced restrictions on the use of valproate including a Pregnancy Prevention Programme

Valproate exposure during pregnancy

- 1 in 10 babies may have a malformation of their body at birth
- 3 or 4 in every 10 children may have serious developmental disorders
- Risk of childhood autism is 5 times more likely compared with the rest of the population
- Children are more likely to have attention deficit hyperactivity disorder (ADHD)

History and overview of the PREVENT Programme

To facilitate EMA restrictions the HSE Chief Clinical Officer commissioned the HSE Valproate Response Project in 2018 to:

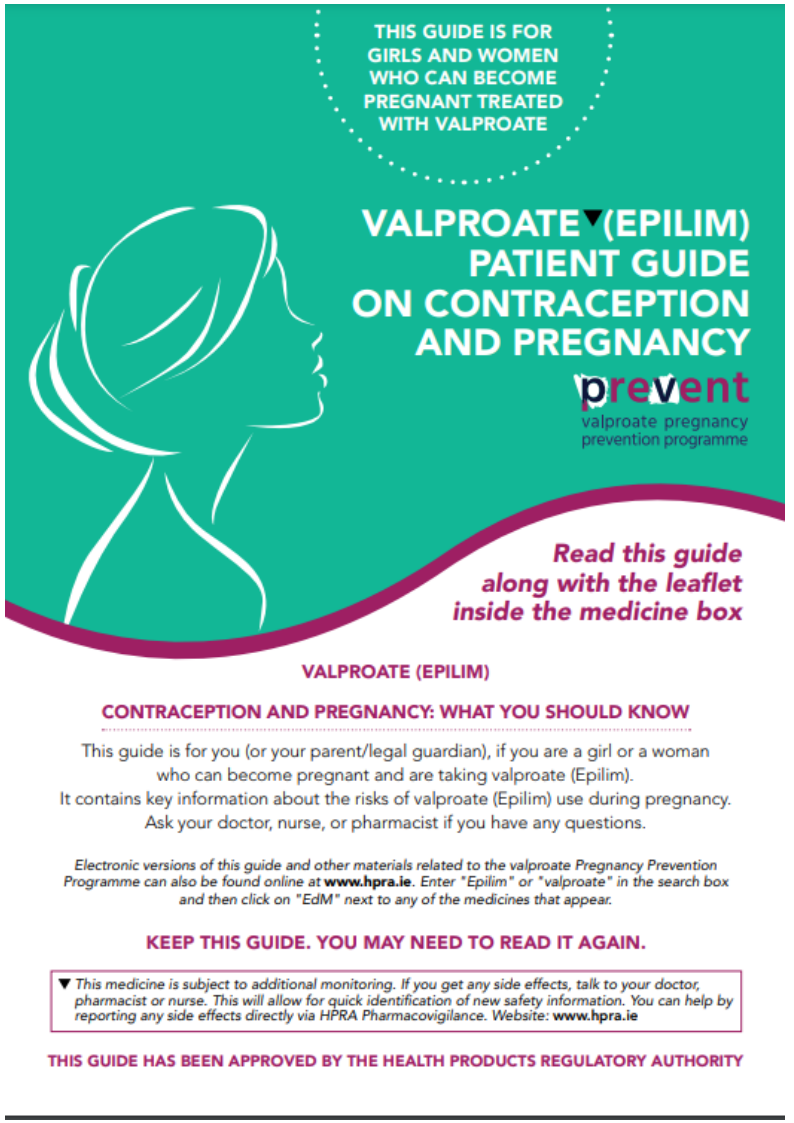
- Ensuring that people who may have been impacted by Valproate exposure in the womb are provided with information and support
- Development of assessment and intervention pathways for children/adults who may have Foetal Valproate syndrome
- Implementation of the Valproate Pregnancy Prevention Programme
- To establish a Programme for Women's Health in Epilepsy

Aims of the PREVENT Programme

- Support implementation of the guidance provided by the HPRA.
- Provide clinical guidance on and ensure availability of information on the risk of Valproate use in girls (of any age), women of child-bearing potential and pregnant women.
- Support communication and collaboration between the clinicians managing the pregnancy prevention programme and those prescribing valproate.
- Support communication and collaboration between the prescribers and the dispensing pharmacists.
- Development of the Epilepsy in Pregnancy Drugs Registry for Valproate to support the HSE implementation of PREVENT.
- Establishment of an Epilepsy Pregnancy Register.

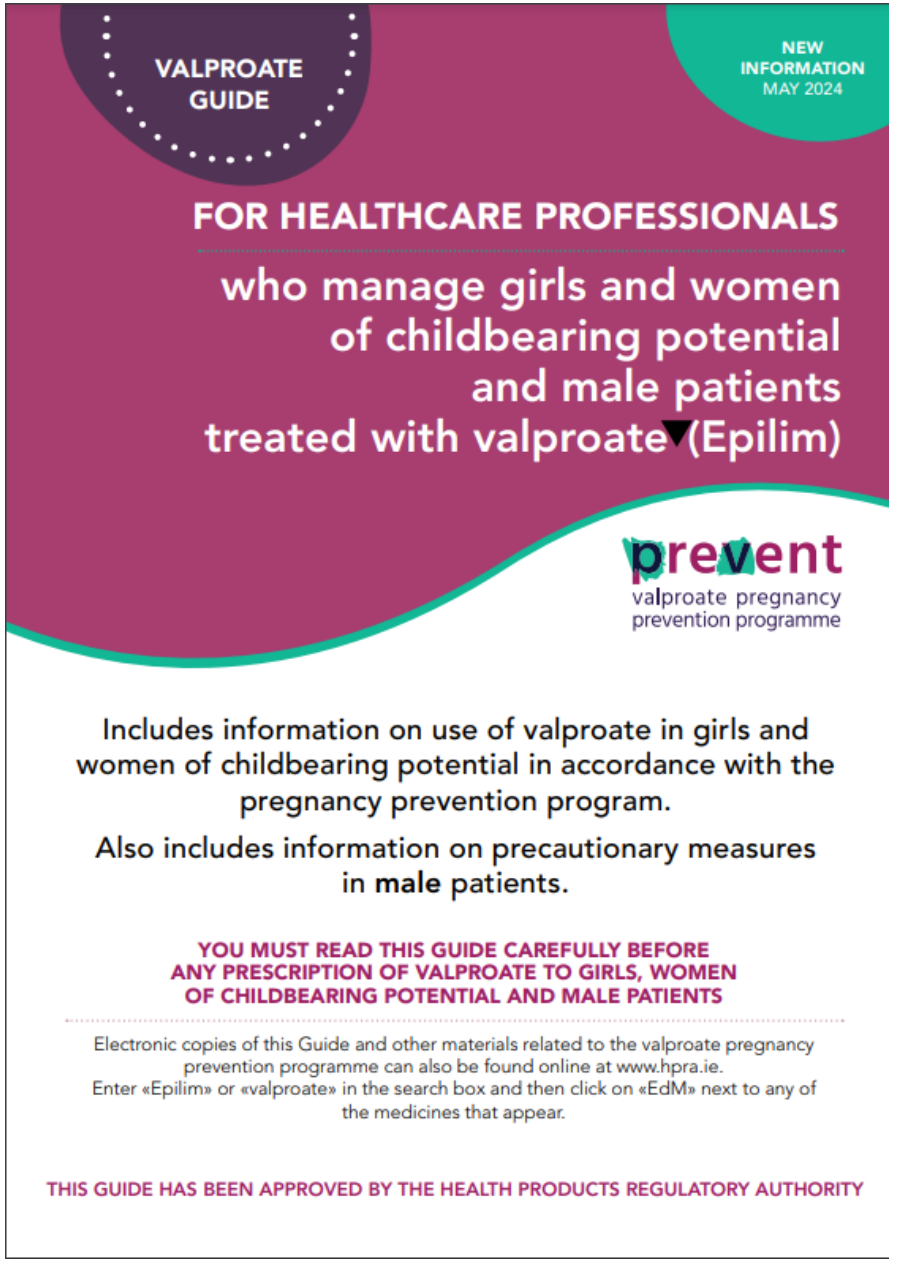
PREVENT HPRA guidance

- Treatment with valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder.
- Valproate must not be used in girls and women of childbearing potential (i.e. those that can become pregnant) unless other treatments are ineffective or not tolerated and the terms of a pregnancy prevention programme, known as 'prevent', are followed.
- Patients have to be reviewed by their specialist annually and the Annual Risk Assessment form has to be completed
- Women of childbearing potential on Valproate have to be on effective contraception



Prescribing Valproate

- Assess patients for pregnancy potential
- Explain the risks of congenital malformations and neurodevelopmental disorders
- Perform a pregnancy test prior to initiation and during treatment as needed
- Counsel on the need for effective contraception throughout the treatment
- Explain the need for pregnancy planning and need to urgently consult her doctor in case of pregnancy
- Provide the Patient Guide and complete the Annual Risk Acknowledgement Form with the patient at initiation and at annual specialist review



Annual Risk Acknowledgement Form
Valproate (Epilim▼) and Risks in Pregnancy

prevent
valproate pregnancy prevention programme

Name of Patient: **Date of Birth:**

MRN:

Name & Role of Specialist:

Name of Patient's GP:

Children exposed to valproate in utero have a very high risk for congenital malformations and neurodevelopmental disorders. Valproate is therefore contraindicated in women of childbearing potential (i.e. a pre-menopausal female who is capable of becoming pregnant) unless the conditions of 'prevent', the valproate (Epilim) pregnancy prevention programme are fulfilled.

- Specialists should complete and sign the Annual Risk Acknowledgement Form (ARAF) with a female patient of childbearing potential treated with valproate.
- The ARAF discussion ensures female patients understand why they are prescribed valproate and the need to prevent pregnancy due to the risks for children exposed in utero.
- Discuss and complete the ARAF at treatment initiation (or when menarche is reached), at the annual visit, or when a pregnancy is planned.
- The ARAF can be completed with a parent/legal guardian when appropriate (e.g. minors, patients without capacity to make an informed decision).
- In cases of pregnancy, the ARAF (part C) can be used as a basis for discussion.
- File the signed ARAF in the patient's medical record and give a copy to the patient and her GP.

Refer to the valproate (Epilim) **HCP guide** for full details on the requirements of **'prevent'**, including use of the ARAF, and provide a copy of the valproate (Epilim) Patient Guide† to patients.

A follow-up appointment should be arranged at least every year to review the need for continued treatment with valproate and adherence to **'prevent'** measures.

A new form must be completed at each annual review.

This form expires on _____ **(12 months after completion).**

† Patient Guide and patient card can be found online at www.hpra.ie by entering "Epilim" or valproate in the 'Find a medicine' search box and then clicking on "EdM" next to any of the medicines that appear.

Annual Risk Acknowledgement Form
Valproate (Epilim▼) and Risks in Pregnancy

prevent
valproate pregnancy prevention programme

Name of Patient: **MRN:**

Part A - Does 'prevent' apply to this patient?

Women of childbearing potential (i.e. pre-menopausal females who are capable of becoming pregnant) taking valproate, regardless of the indication, should fulfil all the requirements of the **'prevent'** pregnancy prevention program. The only exception is when you (the specialist) consider that there are compelling reasons to indicate that there is no risk of pregnancy. When initiating or reviewing treatment, carefully assess the potential for pregnancy and decide if **'prevent'** applies to this patient (see below).

Specialist Assessment	Tick box
The patient is of childbearing potential and **'prevent'** applies (sign Part A and proceed to B and C)	☐
The patient is of childbearing potential, however, there are compelling reasons to indicate there is no risk of pregnancy and the requirements of **'prevent'** do not apply (record reasons here and sign Part A):	☐

Note: If the compelling reason(s) may be subject to change (not permanent), the patient should be advised to contact her specialist immediately if her circumstances change, and a regular review of the reason should be undertaken as part of treatment reviews and at least annually. The patient should be provided with a copy of the patient guide and the risks of pregnancy explained so that she is aware of the risks if circumstances change. Parts B and C of the form can be completed to aid discussion and understanding.

For girls that have not yet reached menarche, parents/legal guardians should be advised of the need to contact the specialist as soon as menarche occurs to arrange for a review of treatment. The patient and/or her parents/legal guardian should be provided with a copy of the patient guide and the risks of pregnancy explained so that they are aware of the risks for the future. Parts B and C of the form can be completed to aid discussion and understanding, where appropriate.

I confirm that, where applicable, I have given the patient (and/or her parent/legal guardian) a copy of the valproate (Epilim) patient guide and informed her that an electronic version of the patient guide, patient card and package leaflet can be accessed at www.hpra.ie†	☐

Name of Specialist:

Signature: _____

Date:

† Patient Guide and patient card can be found online at www.hpra.ie by entering "Epilim" or valproate in the 'Find a medicine' search box and then clicking on "EdM" next to any of the medicines that appear.

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Annual Risk Acknowledgement Form
Valproate (Epilim▼) and Risks in Pregnancy

prevent
valproate pregnancy prevention programme

Name of Patient:		MRN:	

Part B: Specialist acknowledgement that risks related to the use of valproate during pregnancy and the requirements of 'prevent' were discussed with the patient

I confirm I have discussed the following with the patient:	Initials
The patient needs valproate because: ☐ her condition does not respond adequately to other treatments ☐ she does not tolerate other treatments ☐ she is currently undergoing a treatment change from valproate	
Valproate must not be used during pregnancy (except in rare situations in epilepsy for patients who are resistant or intolerant to other treatments)	
The overall risks in children exposed to valproate during pregnancy are: • an approximately 11% chance of major congenital malformations and • up to 30% to 40% chance of a wide range of early developmental problems that can lead to significant learning disabilities	
The conditions of the pregnancy prevention programme must be fulfilled when of childbearing potential	
The need for regular (at least annual) review of the need to continue valproate treatment by a specialist	
The need for a negative (serum) pregnancy test result at treatment initiation and as needed thereafter (when of childbearing potential)	
The need for effective contraception, without interruption, throughout treatment with valproate (when of childbearing potential)	
The need to arrange an appointment with her specialist as soon as she is planning pregnancy to ensure timely discussion, and a timely switch to an alternative treatment before stopping contraception and conception occurring	
The need to contact her doctor immediately for an urgent referral and review of treatment by her specialist in case of suspected pregnancy	
I confirm I have given the patient (and/or her parent/legal guardian) a copy of the valproate (Epilim) patient guide and informed her that an electronic version of the patient guide, patient card and package leaflet can be accessed at www.hpra.ie†	
In case of pregnancy, I confirm that:	
• We have discussed options for switching treatment	
• She is receiving the lowest possible effective dose of valproate to minimise the possible harmful effect on the unborn	
• She is fully aware of the risks of pregnancy	
• She is informed about the possibility of pregnancy support or counselling and appropriate monitoring of her baby during pregnancy	
• I confirm I have given the patient (and/or her parent/legal guardian) a copy of the valproate (Epilim) patient guide and informed her that an electronic version of the patient guide, patient card and package leaflet can be accessed at www.hpra.ie†	
Clinical notes (as applicable):	

Name of Specialist:

Signature: _____ **Date:**

† Patient Guide and patient card can be found online at www.hpra.ie by entering "Epilim" or valproate in the 'Find a medicine' search box and then clicking on "EdM" next to any of the medicines that appear.

Annual Risk Acknowledgement Form
Valproate (Epilim▼) and Risks in Pregnancy

prevent
valproate pregnancy prevention programme

Name of Patient:		MRN:	

Part C: Patient acknowledgement that the risks of valproate use during pregnancy and the requirements of 'prevent' are understood

To be completed by the patient and signed by her (or parent /legal guardian if applicable*) and her specialist	Initials
I have discussed the following with my specialist and I understand:	
• Why I need valproate rather than another medicine	
• That I should visit a specialist regularly (at least once a year) to review whether valproate remains the best option for me	
• If I use valproate while I am pregnant, my baby has significant risk of serious harm	
The overall risks in children whose mothers took valproate during pregnancy are: • approximately 11 babies in every 100 will have birth defects and • up to 30 to 40 children in every 100 may have a wide range of early developmental problems that can lead to significant learning difficulties	
• Why I need a negative pregnancy test at the start of treatment and as needed thereafter	
• The reasons why I must use effective contraception, without stopping or interruption, at all times while taking valproate	
• The options for effective contraception (or a consultation has been planned with a professional who can give me advice)	
• The need to consult my specialist or GP (who will refer me to the specialist) as soon as I start thinking about becoming pregnant. This is to make sure I have time to switch to another treatment before I stop contraception	
• That I should request an urgent appointment with my specialist if I think I am pregnant	
• I have received a copy of the valproate (Epilim) patient guide and understand that I can access www.hpra.ie for an electronic version of the patient guide, patient card or package leaflet†	
In case of pregnancy, I have discussed the following with my specialist and understand:	
• The options for switching treatment	
• The risks of valproate use in pregnancy	
• The possibilities of pregnancy support or counselling	
• The need for appropriate monitoring of my baby	

Name of Patient:

Signature: _____ **Date:**

If applicable, name of person signing on behalf of patient: *

Relationship to patient (parent/legal guardian):

Signature: _____ **Date:**

Name of Specialist:

Signature: _____ **Date:**

* for patients who are minors or without the capacity to make an informed decision.

† Patient Guide and patient card can be found online at www.hpra.ie by entering "Epilim" or valproate in the 'Find a medicine' search box and then clicking on "EdM" next to any of the medicines that appear.

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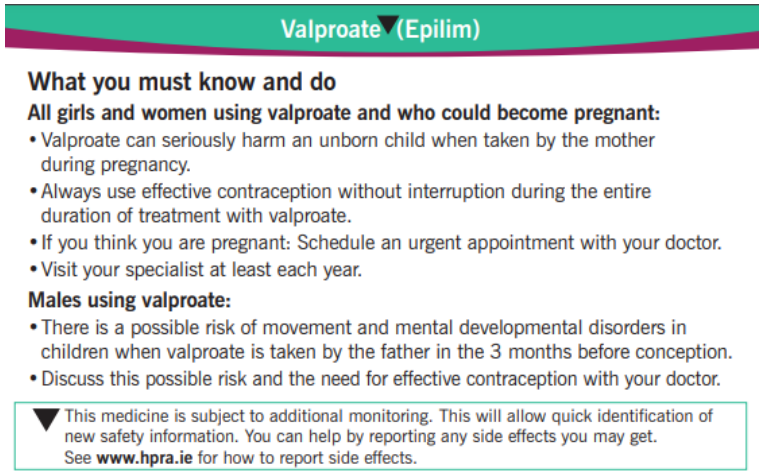
Dispensing Valproate

- Patient card has to be attached to the packaging of valproate each time valproate is dispensed

- A visual warning to inform healthcare professionals and patients about the risks to an unborn child if used during pregnancy is displayed on both the inner blister and outer packaging of valproate medicines.



Valproate▼(Epilim)

What you must know and do

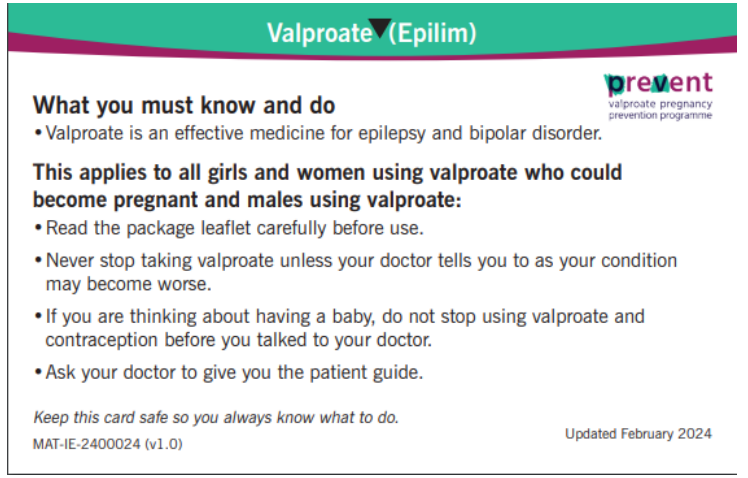
All girls and women using valproate and who could become pregnant:

- Valproate can seriously harm an unborn child when taken by the mother during pregnancy.
- Always use effective contraception without interruption during the entire duration of treatment with valproate.
- If you think you are pregnant: Schedule an urgent appointment with your doctor.
- Visit your specialist at least each year.

Males using valproate:

- There is a possible risk of movement and mental developmental disorders in children when valproate is taken by the father in the 3 months before conception.
- Discuss this possible risk and the need for effective contraception with your doctor.

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See **www.hpra.ie** for how to report side effects.



Valproate▼(Epilim)

prevent valproate pregnancy prevention programme

What you must know and do

- Valproate is an effective medicine for epilepsy and bipolar disorder.

This applies to all girls and women using valproate who could become pregnant and males using valproate:

- Read the package leaflet carefully before use.
- Never stop taking valproate unless your doctor tells you to as your condition may become worse.
- If you are thinking about having a baby, do not stop using valproate and contraception before you talked to your doctor.
- Ask your doctor to give you the patient guide.

Keep this card safe so you always know what to do.

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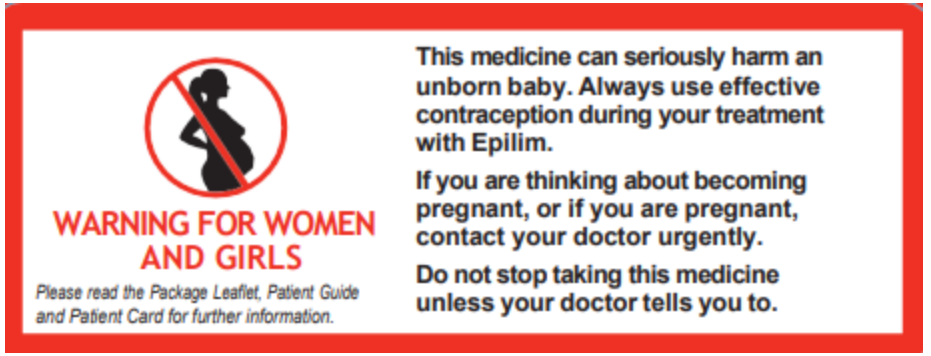
Updated February 2024



WARNING FOR WOMEN AND GIRLS

Please read the Package Leaflet, Patient Guide and Patient Card for further information.

This medicine can seriously harm an unborn baby. Always use effective contraception during your treatment with Epilim.

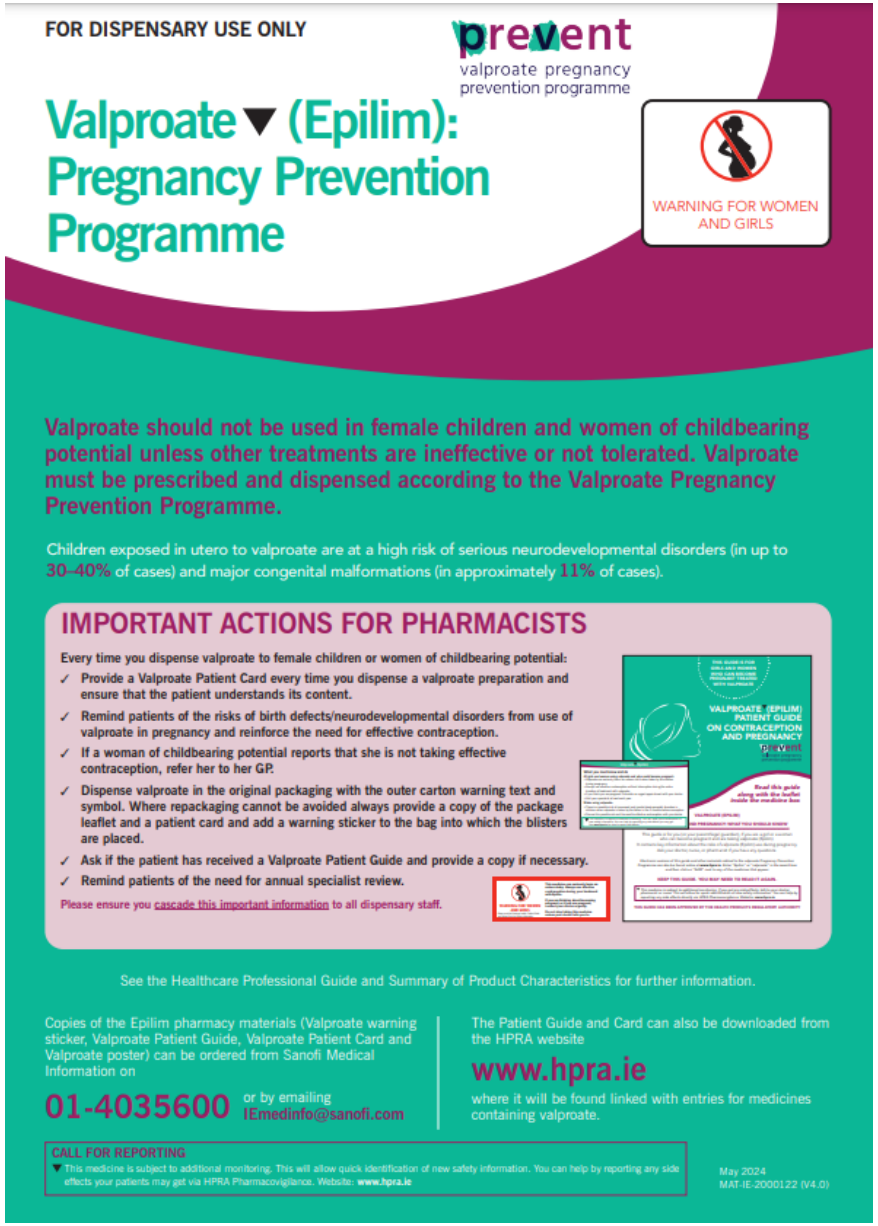
If you are thinking about becoming pregnant, or if you are pregnant, contact your doctor urgently.

Do not stop taking this medicine unless your doctor tells you to.

Dispensing Valproate

Every time you dispense valproate to female children or women of childbearing potential:

- Provide a Valproate Patient Card every time you dispense valproate
- Remind patients of the risks of birth defects/neurodevelopmental disorders from use of valproate in pregnancy and reinforce the need for effective contraception.
- Dispense valproate in the original packaging with the outer carton warning text and symbol.
- Where repackaging cannot be avoided always provide a copy of the package leaflet and a patient card and add a warning sticker to the bag into which the blisters are placed.
- Ask if the patient has received a Valproate Patient Guide and provide a copy if necessary.
- Remind patients of the need for annual specialist review.



Differences to UK guidance

MHRA legislation since 2023:

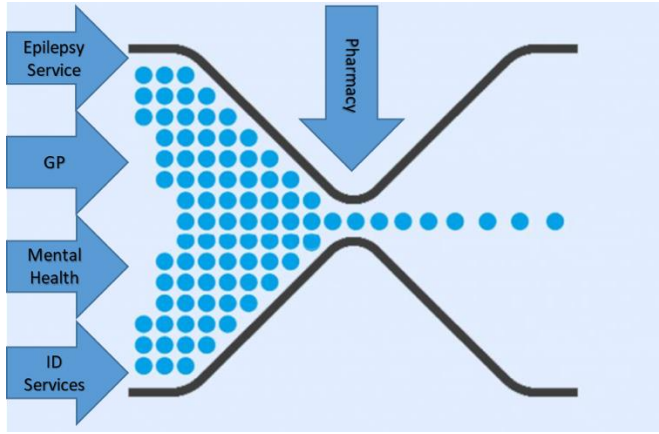
- Valproate must only be dispensed in original full packs, which clearly show the contraindication in pregnancy, including a pictorial warning
- No further initiations of valproate in anyone (male or female) under 55 years of age, unless two specialists independently consider and document that there is no other effective or tolerated treatment
- In women of childbearing potential and girls already taking valproate, a second specialist signature is required at the next annual review if the patient is to continue with valproate

Challenges in delivering PREVENT

- Identifying individual women prescribed Valproate to ensure compliance with the PREVENT programme
- Valproate may be prescribed by GPs, general neurologists, psychiatrists and private practitioners making it difficult to identify all prescribers of Valproate reliably
- As many prescriptions are paper based and the information from prescriptions is not collected at a centralised point there is no way of identifying all women prescribed Valproate in Ireland reliably through their prescriptions
- Ultimately having national electronic prescribing and a unique patient identifier may provide the most reliable solution to identifying all women of childbearing potential prescribed Valproate in Ireland

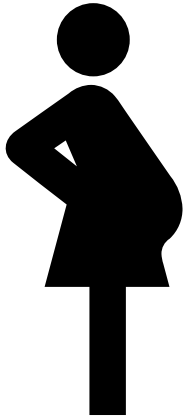
Valproate Registry

- One of the aim of the PREVENT programme is to establish a registry for all women on Valproate in Ireland
- Since the establishment of PREVENT multiple options have been explored
- For example using the National Epilepsy EPR
- Currently we are exploring the auditing of electronic dispensing systems in Ireland to capture all women dispensed Valproate
- In the long-term electronic prescribing will likely be the most sustainable solution to capturing all patients prescribed Valproate and other teratogenic medications



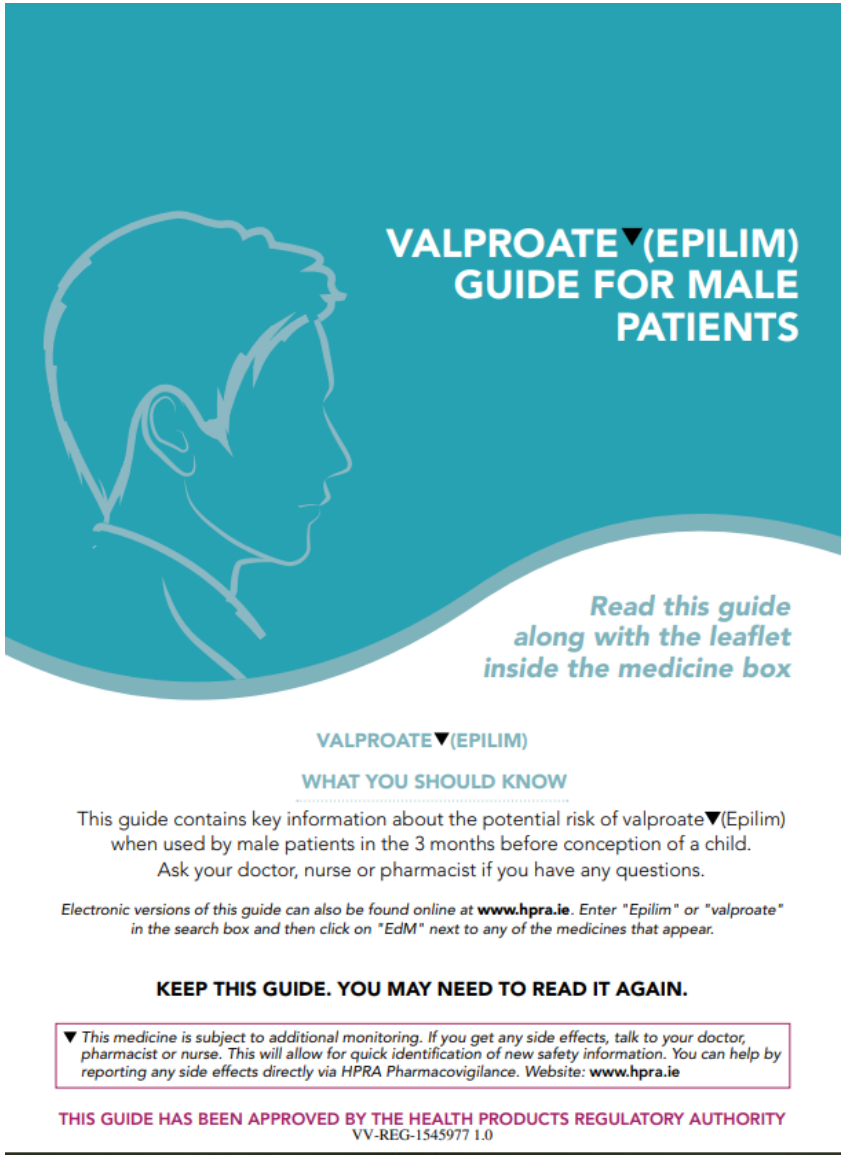
Pregnancy Registry for women with Epilepsy

- Developing a pregnancy registry is one of the aims of the PREVENT programmes
- Currently there is no active Pregnancy Registry for women with Epilepsy in Ireland
- A future registry should ideally be used mandatory and cover all anti-seizure medications and should be linked to a larger National Pregnancy Register
- It should also be linked with international registries – such as EURAP for anti-seizure medications
- Hopefully the HSE “Digital for Care 2030” will help with developing the pregnancy registry



Men and Valproate

- In 2023 the EMA highlighted a study suggesting a possible risk of movement and mental developmental (neurodevelopmental) disorders in children born to fathers treated with valproate (Epilim) in the 3 months before conception
- In this study, around 5 children in every 100 had such disorders when born to fathers treated with valproate (Epilim), compared to around 3 children in every 100 when born to fathers treated with lamotrigine or levetiracetam
- It was recommended that valproate is initiated and supervised by a specialist
- HPRA has developed a patient and prescribers guide guide



VALPROATE▼(EPILIM) GUIDE FOR MALE PATIENTS

Read this guide along with the leaflet inside the medicine box

VALPROATE▼(EPILIM)

WHAT YOU SHOULD KNOW

This guide contains key information about the potential risk of valproate▼(Epilim) when used by male patients in the 3 months before conception of a child.
Ask your doctor, nurse or pharmacist if you have any questions.

Electronic versions of this guide can also be found online at **www.hpra.ie**. *Enter "Epilim" or "valproate" in the search box and then click on "EdM" next to any of the medicines that appear.*

KEEP THIS GUIDE. YOU MAY NEED TO READ IT AGAIN.

▼ *This medicine is subject to additional monitoring. If you get any side effects, talk to your doctor, pharmacist or nurse. This will allow for quick identification of new safety information. You can help by reporting any side effects directly via HPRA Pharmacovigilance. Website:* **www.hpra.ie**

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Men and Valproate

For Prescribers:

- Discuss the potential risk of neurodevelopmental disorders for children born to men treated with valproate in the 3 months prior to conception.
- To consider effective contraception, including for a female partner, while using valproate and for at least 3 months after stopping the treatment.
- Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.
- Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient.
- For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients.

For Pharmacists:

- Ensure the patient received the Patient Guide and Patient Card
- Remind the patient that online information can also be found by scanning the QR code which is included in the patient leaflet and on the outer carton

Resources

HPRA:

https://www.hpra.ie/safety-information/how-we-monitor-safety/medicines/use-of-medicines-in-pregnancy/valproate-(epilim)-use-in-female-patients-of-reproductive-potential-and-during-pregnancy

HSE:

https://www.hse.ie/eng/about/who/cspd/ncps/prevent/