Prescribing of Valproate Containing Products in People Under the Age of 55

Introduction

The Medicines & Healthcare products Regulatory Agency (MHRA) have updated its guidance about valproate use and new regulatory measures have been introduced to reduce avoidable harm from valproate. The restrictions now state that:

- Valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, except if there are compelling reasons that the reproductive risks do not apply; and
- At their next annual review specialist review, female patients of child bearing potential and girls, should be reviewed using the latest Valproate Annual Risk Acknowledgement Form (ARAF)

These regulatory changes are further supported by:

- Smaller pack sizes of valproate to encourage monthly prescribing
- A pictogram / warning image on valproate labelling
- Rules introduced in 2023 to ensure all patients receive the whole pack of valproate with the warnings on the box. DBTH pharmacy labelling standards have been amended to reflect this change.

Paediatric Patients

Responsibilities of consultant paediatrician with a special interest in epilepsy

Before initiation of valproate treatment, the consultant must:

- Consult with patient / carer(s) / parent(s)
- Provide appropriate information to patient / carer(s) / parent(s) Document (medicines.org.uk) Hard copies are available in clinic
- Obtain informed consent to treatment after risks and benefits of treatment explained.

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- Discuss the case with colleague consultant Paediatrician with expertise in epilepsy. That consultant will review the case, if necessary have a discussion with patient and parent and then sign relevant ARAF
- Completed ARAF will be filed in case note, copy given to GP, patient / parent(s)/carer(s) a copy and file on MEDISEC.
- Maintain consultant led care whilst patient on valproate

Paediatric Consultant with expertise in epilepsy will maintain database of patients receiving valproate under their care. The consultant will write (email) to D&T committee secretary in first week of April providing information on annual reviews undertaken in previous 12 months to ensure all appropriate patients receive the review.

Note: FEMALE patients will require an annual completion of the appropriate ARAF form (see appendix I). On subsequent annual reviews, if the patient is to continue on valproate, this can have one specialist signature unless the situation changes.

Note: MALE patients currently only require a Risk Acknowledgement form at initiation (see appendix II)

The second signatory could include the following:

- Epilepsy nurse consultant
- Specialists nurses in relevant disciplines
- Paediatricians with special interest in epilepsy
- Specialty and associate specialist doctors in psychiatry and neurology
- Consultant adult or paediatric neurologists
- Consultant psychiatrists
- Paediatricians who regularly manages complex epilepsy or bipolar disorder.

The second signatory should not be in direct line management of the primary signatory.

Paediatric Patients who are already taking valproate

At the annual review, female patients should be reviewed by the consultant and the appropriate form completed. The process above for new patients should be followed. The first review will require two specialists signatures, subsequent review will require only one specialist unless the patients situation changes.

Male patients do not require the ARAF form to be completed if already initiated on valproate prior to January 2024 but they and their carer(s) / parent(s) should be made aware of the risk of male infertility and given the Patient Guide Document (medicines.org.uk)

New Adult Patients & Valproate

Valproate containing products should only be initiated by specialists in psychiatry and neurology. For patients aged 55 years and under, who valproate may be considered, this would need to be under specialist care though visiting consultants, and they would be responsible for completing the appropriate ARAF and associated responsibilities.

The annual risk acknowledgement forms are also available as a link from the DBTH pharmacy formulary page. Please ensure you are using the most up-to-date version of this form.

Appendix I Annual Risk Acknowledgement Form FEMALE Patients

Annual Risk Acknowledgement Form for Female Patients
VALPROATE HAS RISKS IN PREGNANCY

Children exposed to valproate during pregnancy have a high risk for congenital malformations and neurodevelopmental disorders which may lead to permanent disability.

Valproate should not be used in female patients aged under 55 years unless two specialists (specialist prescriber and countersigning specialist) independently consider and document, in this form, that there is no other effective or tolerated treatment. This form outlines the conditions of prevent - the valproate Pregnancy Prevention Programme and when these must be fulfilled.

Female patients who have a permanent reason that they do not have the potential to get pregnant (e.g., post-menopausal patients or those after hysterectomy) do not need to complete this form beyond step 1. This form can be used to support documentation in the medical notes that prevent does not apply to this patient.

- This form is used to support and record the prescribing decision and, where applicable, discussion with the patient or their responsible person of the risks associated with the use of valproate during pregnancy and the measures needed to minimise the risks in female patients.
- The specialist prescriber must provide this form to female patients treated with valproate (Epilim, Depakote, Convulex, Episenta, Epival, Sodium Valproate, Syonell, Belvo & Dyzantil) – or to their "responsible person" i.e., a parent/legal guardian or person capable of giving consent on behalf of patients who are minors or without the capacity to make an informed decision, or a person acknowledging that the treatment is in the best interests of the patient.
- The decision of the countersigning specialist must be documented in step 2. A countersigning specialist is only required for patients newly starting valproate and for existing female patients at one annual review. Subsequent annual reviews do not require the countersigning specialist unless the patient's circumstances have changed.

Once completed, a copy of this form should be given to the patient or their responsible person and stored in their medical notes, it should also be shared with all healthcare professionals listed in the table below.

Name of patient:	**Patient's date of birth:**
Patient's NHS number:	**Patient's hospital number:**
Name and contact details of specialist prescriber:	**Role and unique identifier:**
Signature of specialist prescriber:	**Date of signature:**
Name of countersigning specialist:	**Role and unique identifier:**
Signature of countersigning specialist (If needed specialist prescriber can sign here to confirm that discussion with countersigning specialist has occurred):	**Date of signature:**
Name and address of patient's General Practitioner (GP):	
Date form completed:	

WARNING: Prescribing valproate to a woman of childbearing potential without the conditions of **prevent - the Pregnancy Prevention Programme** being fulfilled is contraindicated and represents an unlicensed use of the drug. Use of valproate during pregnancy for bipolar disorder, and during pregnancy for epilepsy (unless there is no other effective or tolerated treatment), are both unlicensed. This is the case even when treatment is based on an informed choice made by the patient.

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines listed.

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Annual Risk Acknowledgement Form for Female Patients
VALPROATE HAS RISKS IN PREGNANCY

Step 1 – Specialist prescriber: Establish whether the patient is at risk of the reproductive harms of valproate

The following issues should be considered when evaluating the risks associated with the use of valproate during pregnancy:

- Women of childbearing potential (from menarche to menopause) who are taking any medicine containing valproate, regardless of the indication, should fulfil all the conditions of **prevent** unless there are compelling reasons that there is no risk of pregnancy which should be documented below.
- If the potential for not becoming pregnant is permanent, the reason should be documented below and the conditions of **prevent DO NOT** need to be fulfilled.
- Female children who have not yet reached menarche (not started her periods) **DO NOT** need to fulfil the conditions of **prevent**, but they and their responsible person need to be aware of the risks for the future. You should provide a copy of the Patient Guide and remind the responsible person to contact their GP once the female child using valproate experiences menarche. Their GP will refer the patient back to the specialist prescriber.
- If the compelling reason(s) suggesting no risk of pregnancy may be subject to change, the risks should be discussed at subsequent annual reviews or sooner if their circumstances change.

If you consider there is a reason that indicates **prevent** does not apply, *tick* which reason applies and record here. If the reason is permanent, steps 2, 3 and 4 do not need to be completed.

To be completed by the specialist prescriber if they consider prevent - the Valproate Pregnancy Prevention Programme (PPP) - is not needed
☐ The patient has not yet reached menarche at the time of this appointment. I have asked the patient and their family to inform their GP to refer the patient back to the specialist prescriber if this changes before their next annual review.
☐ The absence of pregnancy risk is considered to be permanent for the following reason (*insert reason*):
☐ There are other reasons that conditions of **prevent** are not applicable (*insert reason*):

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines listed.

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Annual Risk Acknowledgement Form for Female Patients
VALPROATE HAS RISKS IN PREGNANCY

Step 2: Specialist prescriber and countersigning specialist: Document the prescribing decision.

Actions to be completed by the specialist prescriber to confirm the prescribing decision	Initial to confirm all that apply
• The patient's condition does not respond to other treatments or other treatments are not tolerated.	
• I have discussed the risks with the patient, and I consider the balance of benefits and risks to be favourable.	
• I have offered the patient a copy of the Patient Guide and they know where to get further information.	
• The patient is in the process of changing treatment away from valproate.	

To be completed by the countersigning specialist (can be completed by specialist prescriber following discussion with countersigning specialist if needed)	Initial to confirm all that apply
• I confirm that this patient should be treated with valproate.	
• The patient's condition does not respond to other treatments or other treatments are not tolerated.	
• The patient has been informed of the risks and I consider the balance of benefits and risks to be favourable.	
• The patient is in the process of changing treatment away from valproate.	

Step 3: Specialist prescriber: Explain the risks to the patient or responsible person.

The risks must be discussed with the patient or their responsible person (if applicable), and the patient (or responsible person) must sign the subsequent section of this form to confirm they have discussed and acknowledge the risks of taking valproate during pregnancy.

Information to be discussed with the patient or their responsible person	Initial to confirm you have discussed
That their medication should be reviewed regularly (at least once a year) and their medication may need to be changed if their circumstances change, increasing the risks.	
That valproate can cause serious harm to an unborn baby if taken by a mother during pregnancy, which may lead to permanent disability. The overall risks in children exposed to valproate during pregnancy are: • an approximately 11% chance of physical birth defects • up to a 30% to 40% chance of neurodevelopmental disorders	
Explain the conditions of **prevent - the Pregnancy Prevention Programme** and why these must be fulfilled.	
The need for a negative (ideally serum) pregnancy test result before starting treatment with valproate and, if needed, further pregnancy tests at appointments thereafter.	
The need to use effective birth control (contraception), without interruption, throughout treatment with valproate.	
The need to consult their general practitioner (GP) for referral to the specialist as soon as they are planning pregnancy to ensure timely discussion and switching to another treatment before the child is conceived and before birth control (contraception) is discontinued.	
The need for the patient to contact their GP immediately, to be urgently referred to their specialist prescriber for an urgent review of their treatment in case of suspected or unplanned pregnancy.	
Explain the risks of stopping valproate without medical advice. Patients on valproate should not stop taking their medicine or change their dose unless they are told to do so by a specialist. This is because their condition may become worse, including an increase in seizures in patients treated for epilepsy and an increased risk of relapse in patients treated for bipolar disorder.	

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines listed.

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Annual Risk Acknowledgement Form for Female Patients
VALPROATE HAS RISKS IN PREGNANCY

Step 4: To be completed by the patient or responsible person

Completing this section of the form confirms that you, the patient (or your responsible person), have discussed and acknowledge the risks of using valproate during pregnancy and the measures needed to reduce the risk with your specialist prescriber.

It is recommended that you keep a copy of this form which will also be added to your medical notes.

I have discussed the benefits and risks of valproate compared to other treatments with my specialist prescriber and I acknowledge that:	**Initial to confirm you acknowledge each item**
My medication should be reviewed regularly (at least once a year) and may need to be changed depending on my circumstances.	
Valproate can cause serious harm to an unborn baby if taken by a mother during pregnancy and may lead to permanent disability. The risks in children whose mothers took valproate during pregnancy are: • An approximately 11% chance of physical birth defects • Up to 30% to 40% of children may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory, or problems with development (behaviour and learning disorders) which can be seriously debilitating and/or permanent.	
I am aware of the need to have a negative pregnancy test before starting treatment with valproate and if needed, further pregnancy tests at subsequent appointments.	
I am aware of the need to use an effective method of birth control (contraception), without stopping or interruption, while taking valproate.	
The options for effective long-term methods of birth control (contraception) have been discussed (or a consultation has been planned with a professional who can give me advice).	
I need to consult my GP to be referred to my specialist prescriber as soon as I start thinking about becoming pregnant. This is to make sure I have time to switch to another treatment before I come off birth control (contraception).	
I should request an urgent appointment with my GP, to be urgently referred to my specialist prescriber, if I think I am pregnant.	
I have been offered a copy of the valproate Patient Guide and know where to find more information online using the QR code on the leaflet in the pack.	
I should not stop valproate or change the dose unless told to do so by my specialist as my condition may become worse, including an increase in seizures in patients treated for epilepsy and an increased risk of relapse in patients treated for bipolar disorder.	
Name of patient:	
Name of responsible person (if applicable):	
Signature of patient (or responsible person):	**Date:**

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines listed.

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Appendix II Risk Acknowledgement Form for MALE patients

Risk Acknowledgement Form
FOR MALE PATIENTS STARTING VALPROATE

This form is used for new male patients starting a medicine containing valproate.

Valproate should not be started in male patients aged under 55 years unless two specialists consider and document that there is no other effective or tolerated treatment or the risk of infertility or potential risk of testicular toxicity do not apply.

This form applies to male patients aged under 55 years because this is the age group most likely to be affected by the risk of infertility and the potential risk of testicular toxicity. However, if these risks do not apply (e.g., the patient is permanently infertile), the countersigning specialist is not required, and the specialist prescriber should use this form to document the reason and record in the patients notes.

- This form is to support and record the discussion of risks with male patients aged under 55 years starting treatment with valproate or their responsible person or parents/care givers (if applicable).
- The specialist prescriber must provide this form to male patients aged under 55 years being started on valproate (Epilim, Depakote, Convulex, Episenta, Epival, Sodium Valproate, Syonell, Belvo & Dyzantil) – or to their "responsible person".
- In this instance, a responsible person is a parent/legal guardian or person capable of giving consent on behalf of patients who are minors or without the capacity to make an informed decision, or a person acknowledging that the treatment is in the best interests of the patient.
- The countersigning specialist must document their decision.

Once completed, a copy of this form should be given to the patient or their responsible person and stored in their medical notes, it should also be shared with all healthcare professionals listed in the table below.

Name of patient:	**Patient's date of birth:**
Patient's NHS number:	**Patient's hospital number:**
Name and contact details of specialist prescriber:	**Role and unique identifier:**
Signature of specialist prescriber:	**Date of signature:**
Name of countersigning specialist:	**Role and unique identifier:**
Signature of countersigning specialist (if needed specialist prescriber can sign here to confirm that discussion with countersigning specialist has occurred):	**Date of signature:**
Name and address of patient's GP:	
Date form completed:	

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Step 1: Specialist prescriber and countersigning specialist: Document the prescribing decision

Actions to be completed by the specialist prescriber to confirm the prescribing decision	Initial to confirm all that apply
• The patient's condition does not respond adequately to other treatments or other treatments are not tolerated.	
• I have discussed the risks with the patient, and I consider the balance of benefits and risks to be favourable.	
• I have offered the patient a copy of the Patient Guide and they know where to get further information.	
• The risk of infertility or potential risk of testicular toxicity do not apply for the following reason(s):	

To be completed by the countersigning specialist prescriber (can be completed by specialist prescriber following discussion with countersigning specialist, if needed)	Initial to confirm all that apply
• Their condition does not respond to other treatments or other treatments are not tolerated.	
• They have been informed of the risks and I consider the balance of benefits and risks to be favourable.	

Step 2: Specialist prescriber: Explain the risks to the patient or responsible person

Information to be discussed with the patient or responsible person	Initial to confirm you have discussed
Fertility while on valproate • Valproate may cause infertility in some male patients. This can make it difficult to have a baby. • Male infertility may be reversible after valproate is stopped or after a dose reduction in some patients.	
Effects on male reproductive system • Some studies in male animals have shown valproate to have an adverse effect on parts of the male reproductive system. These include toxic effects on the testes (testicles). • The weight of the developing testes (testicles) was lower in young animals given valproate and it is unclear what this means for humans.	
Risks of stopping valproate without medical advice • Patients on valproate should not stop taking their medicine or change their dose unless they are told to do so by a specialist. • This is because their condition may become worse, including an increase in seizures in patients treated for epilepsy and an increased risk of relapse in patients treated for bipolar disorder.	

Step 3: To be completed by the patient or responsible person

Completing this section of the form confirms that you, the patient (or your responsible person), have discussed and acknowledge the risk of male infertility, and the toxic effect of valproate on the testes of animals using valproate.
It is recommended that you keep a copy of this form which will also be added to your medical notes.

I have discussed the benefits and risks of valproate compared to other treatments with my specialist prescriber and I acknowledge that:	Initial to confirm you acknowledge each item
• Valproate may cause infertility in some male patients and that this infertility may be reversible after valproate is stopped or after the dose is reduced for some patients.	
• There are animal studies showing that valproate may have an effect on testes (testicles) and it is unclear what this means for humans.	
• I should not stop valproate or change the dose unless told to do so by my specialist as my condition may become worse, including an increase in seizures in patients treated for epilepsy and an increased risk of relapse in patients treated for bipolar disorder. • If my condition becomes worse, I should contact my specialist straight away.	
• I have been offered the Patient Guide and know where I can access this information online using the QR code on the leaflet in the pack.	
Name of patient:	
Name of responsible person (if applicable):	
Signature of patient (or responsible person):	**Date:**

References

1) Valproate: Important new regulatory measures for oversight of prescribing to new patients and existing female patients CEM_CMO_2024_001- (1).pdf
2) Annual Risk Acknowledgement Form for Female Patients Annual Risk Acknowledgement Form for Female Patients.pdf
3) Valproate: review of safety data and expert advice on management of risk November 2023 Valproate-report-review-and-expert-advice.pdf (publishing.service.gov.uk)
4) Risk Acknowledgement form for MALES Document (medicines.org.uk)
5) Annual Risk Acknowledgement for Female patients Document (medicines.org.uk)