VALPROATE PRESCRIBING POLICY

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The latest approved version of this document is online.
If the review date has passed, please contact the Author for advice.

Powys Teaching Health Board is the operational name of Powys Teaching Local Health Board
Bwrdd Iechyd Addysgu Powys yw enw gweithredol Bwrdd Iechyd Lleol Addysgu Powys

Version Control

Version	Summary of Changes/Amendments	Issue Date
V1	Initial Issue	04/02/2025

ENGAGEMENT & CONSULTATION

Key Individuals/Groups Involved in Developing this Document

Role / Designation
Mo Abdelkafi – Medicines Safety Officer (MSO)
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Circulated to the following for Consultation

Date	Role / Designation
6/9/24	All members of PTHB Valproate oversight group
30/9/24	Learning Disabilities service team
23/10/24	Medical Director, Local Medical Committee

Evidence Base
Please list any National Guidelines, Legislation or Health and Care Standards relating to this subject area? Natpsa_2023_013_MHRA.pdf MHRA letter Jan 24 - Direct Healthcare Professional Comms - Oral valproate containing medicines.pdf 05-03-2024_CEM CMO 2024 001_.pdf Follow up to NatPSA_2023_013_MHRA.pdf Valproate use in men: as a precaution, men and their partners should use effective contraception - GOV.UK (www.gov.uk)

IMPACT ASSESSMENTS

Equality Impact Assessment Summary

	No impact	Adverse	Differential	Positive
Age	X			
Disability	X			
Gender reassignment	X			
Pregnancy and Maternity				X
Race	X			
Religion or Belief	X			
Sex			X	
Sexual Orientation	X			
Marriage and Civil Partnership	X			
Welsh Language			X	

Statement

Currently, there is no Welsh language version available for the suggested format of the invitation appointment letter for the annual review (Appendix B) or the easy-read letter (Appendix C). To expedite the publication of this critical policy, these versions should be provided after publication. Where needed, the relevant professional accessing the letters should make attempts to adjust the document.

The aim of this policy is to implement national safety recommendations to stop the risk of valproate products being used in pregnancy and therefore mitigate risk to any child born.

Male and females are treated differently in accordance with this policy, but this is to ensure no risk of pregnancy during valproate treatment.

A woman of childbearing potential in whom pregnancy is a potential will not be able to access valproate treatment and other treatment options will need to be used. This is in line with national safety recommendations.

Risk Assessment Summary

Have you identified any risks arising from the implementation of this policy / procedure / written control document?

The implementation of this policy may cause an increase in workload and burden on services. It may also pose a risk that patients are not able to access specialist services. These issues were discussed with the relevant teams during the development of this policy and will be considered as part of the implementation within these services and teams.

Have you identified any Information Governance issues arising from the implementation of this policy / procedure / written control document? No risks identified.
Have you identified any training and / or resource implications as a result of implementing this? Relevant clinical teams to disseminate this policy. Medicine safety group will engage, inform and advise clinical teams on this policy. The need for specific training is mitigated as resources are linked within this document.

1 Introduction

Valproate is approved in the UK to treat epilepsy and bipolar disorder. It is available in three formulations in the UK: sodium valproate, valproic acid and semisodium valproate. Brands used in the UK include Epilim, Depakote, Convulex, Episenta, Epival, Syonell, Belvo & Dyzantil. It is also sometimes used outside of licence ('off label') to treat other conditions.

Females
Since 2018, valproate has been contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme (PPP) are followed. This is designed to make sure patients are fully aware of the risks and the need to avoid becoming pregnant.

In women who take valproate while pregnant, around 1 in 9 babies (11%) will have a birth defect. Birth defects seen when mothers take valproate during pregnancy include:

- spina bifida (where the bones of the spine do not develop properly)
- facial and skull malformations (including cleft lip and palate)
- malformations of the limbs, heart, kidney, urinary tract and sexual organs

In women who take valproate while pregnant, about 30-40% of children may have neuro developmental problems, and these disorders can be seriously debilitating and permanent. The effects on development can include:

- being late in learning to walk and talk
- lower intelligence than other children of the same age
- poor speech and language skills
- memory problems.

Children exposed to valproate in the womb are three times more likely to develop Autistic spectrum disorders compared with an unexposed population. There is also some evidence children may be more likely to be at risk of developing attention deficit hyperactivity disorder (ADHD)

Males
Valproate administration may also impair fertility in men. The MHRA Drug Safety Update (August 2023), suggests an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception. As a precaution, it has been advised by the MHRA that male patients who are planning a family within the next year, should discuss treatment options with a healthcare professional. Further updates from the MHRA are expected to follow after a re-analysis of the study reviewed.

2 Objective

The MHRA have published safety and educational materials to support the new regulatory measures announced in the National Patient Safety Alert Natpsa/2023/013/MHRA issued 28th November 2023.

Due to the known significant risk of serious harm to a baby after exposure to valproate in pregnancy, these measures aim to ensure **valproate is only used if other treatments are ineffective or not tolerated**, and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme (PPP). Given these and other risks of valproate, these measures also aim to reduce initiation of valproate in patients for whom no other therapeutic options are suitable.

The regulatory change in January 2024, for oral valproate medicines, means that:

A. 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, or there are compelling reasons that the reproductive risks do not apply (see section 5.13 'Specific Patient Groups' within this policy which addresses examples of female patients where conditions of the PPP do not need to be fulfilled).

B. At their next annual specialist review, women of childbearing potential and girls should be reviewed using a revised valproate Risk Acknowledgement Form, which will include the need for a second specialist signature if the patient is to continue with valproate and subsequent annual reviews with ONE SPECIALIST unless the patient's situation changes.

A drug safety update issued in September 2024 indicated a possible association between valproate use by men around the time of conception and an increased risk of neurodevelopmental disorders in their children. The MHRA advise informing male patients who may father children of this possible increased risk and the recommendation for men taking valproate and their partners to use effective contraception during valproate treatment and for at least 3 months after stopping valproate.

3 Definitions

New valproate prescription - Refers to individuals being commenced on valproate for the first time, or when there has been more than 3 month's break in therapy.

Specialist Prescriber – Consultant Psychiatrist.

Primary Prescriber – Medical Consultant working in Mental health or Learning disabilities.

Second Specialist Signatory – Specialist Prescriber or appropriately trained Nurse, Pharmacist or allied health professional working within mental health or learning disabilities specialty services.

Risk Acknowledgement Form* - These forms are used to support and record the prescribing decision and the discussion of associated risk(s) with patient and/or their responsible person. The form used for females also outlines conditions of PREVENT: Pregnancy Prevention Programme.

Annual Risk Acknowledgement Form - used for female patients starting valproate and at their annual review.

**Separate forms used for male and female patients.*

Responsible Person - 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.

Abbreviations

- **ARAF –** Annual Risk Acknowledgement Form
- **MDS –** Monitored Dosage System
- **MH –** Mental health
- **MHRA –** Medicines & Healthcare products Regulatory Agency
- **MSG –** Medicines safety group
- **MSO –** Medicines safety officer
- **PODs –** Patient's Own Drugs
- **PPP –** Pregnancy Prevention Programme
- **PTHB –** Powys Teaching Health Board
- **RAF –** risk acknowledgement form
- **TTO –** To Take Out; a patients medicines prepared for discharge.
- **WCP –** Welsh Clinical Portal
- **WCCIS -** Welsh Community Care Information System

4 Responsibilities

	Staff Group or Specific Role
	All PTHB Employed staff must act in accordance with the PTHB Medicines Policy: (Medicines Policy - Approved V7.docx)

	Commissioned Services – to have processes and delivery plan in place to implement the MHRA National Patient Safety Alert and further updates: Valproate safety measures - GOV.UK (www.gov.uk). **GP / Primary care practitioners** – Read and act in accordance with the Healthcare Professional guide which clearly outlines the roles and responsibilities for GPs. **Pharmacy professionals** - Read and act in accordance with the Healthcare Professional guide. **Community pharmacists** - Read and act in accordance with the Healthcare Professional guide. **All Prescribers** - Read and act in accordance with the Healthcare Professional guide. Must be satisfied that an ARAF/RAF is in place when prescribing. **Midwives –** Should be aware of this policy in order to ensure that patients prescribed valproate are being correctly managed (i.e. known to medic where applicable/ have a ARAF/RAF) **Sexual health teams –** Should be aware of this policy in order to ensure that patients prescribed valproate are being correctly managed (i.e. known to medic where applicable/ have a ARAF/RAF) **Clinical directors** – Ensure clinical teams are aware of the Policy and are practicing in line with the measures. Ensure that a second opinion system is available and accessible. Ensure that clinicians are aware of the teratogenic risks of valproate prescribing in males and females. **All mental health (MH) staff -** Should be aware of this policy in order to ensure that patients prescribed valproate are being correctly managed (i.e. known to medic where applicable/ have a ARAF/RAF). **Medical secretaries -** Must know how to upload the completed ARAF/RAF to the appropriate digital system (WCCIS / WCP). **Consultant Psychiatrists & Specialist prescribers –** Read and act in accordance with Healthcare Professional guide . Ensure that two clinicians independently agree that valproate is the only effective or tolerated treatment available for any new patient (male and female) being started on valproate. Ensure that the patient is made aware of the risks of taking valproate in pregnancy and in male fertility. Ensuring mechanisms are in place for minimum annual review of patients with an ARAF.

	Ensure that mechanisms are in place to effectively communicate this with primary care colleagues (particularly GP). Know what to do if patients are not attending review appointments/ not compliant with ARAF. **Second specialist signatory –** Read and act in accordance with the Healthcare Professional guide. Independently review information provided by the primary prescriber and agree, in their professional opinion that other treatment options have been ineffective, have not been tolerated or would not be tolerated.

5 Prescribing valproate

PREVENT (Pregnancy Prevention Programme, PPP) is supported by the following safety and educational materials available from the MHRA online. This is a collection of information and guidance for healthcare professionals and patients on the reproductive risks of valproate and the new safety measures introduced to reduce these risks.

Healthcare professional **MUST** access and utilise these appropriately in the process of prescribing and reviewing patients on valproate and ensure compliance with PREVENT (PPP).

Safety & Educational materials:

Valproate safety measures - GOV.UK (www.gov.uk)

Patient guide Provides those taking valproate (or their parent, caregiver, or responsible person) with information on the risks of valproate in pregnancy and the risks to male patients and what they need to do.

Healthcare Professional guide Provides updated information for healthcare professionals on the risks of valproate in pregnancy and the risks for male patients, the new conditions for valproate prescribing and key points for patient discussions.

Annual Risk Acknowledgement Form For female patients starting valproate and at annual review. Used to support and record the discussion between the patient and specialist prescriber on the risks associated with valproate in pregnancy and to record the decision of the countersigning specialist. At subsequent annual reviews only one specialist is required.

Risk Acknowledgement form for male patients starting valproate Used to support and record the discussion between the patient and specialist prescriber of the risks associated with valproate in males when starting treatment with valproate and to record the decision of the countersigning specialist. This is only to be completed at initiation of valproate.

Patient card Provides key information for female patients receiving valproate on contraception and pregnancy prevention.

Pharmacy poster Provides important actions for pharmacists dispensing valproate to female patients.

Warning stickers To be added to packaging of medicine in exceptional circumstances where the original pack cannot be dispensed.

No one should stop taking valproate without advice from a specialist. This is because epilepsy or bipolar disorder may become worse without treatment, which can be harmful.

Further resources are available on the PTHB website - resources for patients, resources for healthcare professionals, background and the work of the PTHB valproate oversight group.

5.1 Prevent: Pregnancy Prevention Programme

All Healthcare professionals (Specialist prescribers, General Practitioners and Pharmacists) **MUST** read the Healthcare Professional guide to ensure they have a comprehensive understanding of the PREVENT; Pregnancy Prevention Programme (PPP) and their individual roles and responsibilities to ensure compliance.

Valproate medicines must NOT be used in women of childbearing potential unless the PREVENT: Pregnancy Prevention Programme (PPP) is in place. The conditions of the PPP must be met even for female patients who are not sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Please see section 5.13 'Specific Patient Groups' within this policy which addresses examples of female patients where conditions of the PPP do not need to be fulfilled.

The PPP is a system of ensuring all female patients of childbearing potential taking valproate medicines:

- Have been told about and understand the risks of use in pregnancy and have signed a Risk Acknowledgement Form.
- Are on effective contraception as detailed within PREVENT: PPP, at least one effective method of contraception, preferably a highly effective user independent form such as an intra-uterine device or implant or two complementary forms of contraception including a barrier method should be used.
- See their specialist at least once a year.

- The PPP incorporates use of the safety and education materials as detailed in the previous section, when valproate is prescribed for a girl (of any age) or women of childbearing potential.

In addition, further measures to support from a safety perspective include:

- smaller manufacturer medication pack sizes to encourage monthly prescribing.
- a pictogram/warning image on valproate labelling.
- legislation introduced in 2023 to ensure all patients receive an original pack of valproate with the warnings on the box.

5.2 Valproate prescribing checklist

Specialist prescribers making recommendations for treatment, must always carefully balance the benefits of valproate treatment against the risks. Valproate should only be used when other treatment options have been ineffective, have not been tolerated or would not be tolerated, as judged by an experienced specialist.

The following actions must be completed by anyone who prescribes valproate, or who makes a recommendation for valproate to be prescribed, for a particular patient:

A: Access the MHRA Valproate safety measures as listed in section 5 of this policy

- Read the Healthcare Professional guide
- Provide the patient with a copy of Patient guide to support them to make an informed choice.
- Complete the relevant Risk Acknowledgement form, with a clear understanding when a second specialist signatory is required.

B: Second Specialist Signatory

- To check if a Second Specialist Signatory is required to sign the Risk Acknowledgment Form, i.e. that this is a new prescription for valproate in a male or female patient under 55 years of age.
- Independently review information provided by the primary prescriber and agree, in their professional opinion that other treatment options have been ineffective, have not been tolerated or would not be tolerated. See section 5.6 Prescribing valproate – second specialist signatory requirements for further information on the process to follow if the second signatory disagrees with the decision to prescribe valproate.

C: Assess capacity

- Assess the patient's capacity to understand the requirements and consent to treatment with valproate and document the outcome of this assessment in the patient's notes.

- Refer to sub-section 5.11 Patients who are assessed to lack capacity in this policy.

D: Check if pregnancy test needed

- Perform serum pregnancy test at least 14 days after last possible date on which patient had, or could have had, unprotected sex.
- For further details see sub section 5.9 Pregnancy testing of this policy
- Note valproate is contraindicated for women with bipolar disorder who are pregnant with no option for two specialists to override this (or something similar).

E: Contraception arrangements

- The prescriber must arrange for effective contraception (as defined within the PREVENT: PPP; see the Health Care Professional Guide) to be active for women of childbearing potential **before** the first prescription is issued. There may be temporary exceptions to this whilst the patient is in an INPATIENT setting, whereby there are safeguards to mitigate against the risk of pregnancy. However, females of childbearing potential must be on effective contraception before home leave or being discharged on valproate
- Refer to sub-section 5.10 Contraception advice within this policy

F: Prescribe Folic acid

- All women of childbearing potential and girls who are prescribed valproate and are planning or considering pregnancy should also be prescribed folic acid 5mg daily.

G: Resources

- It is the prescriber's responsibility to access most recent version of relevant resources to support prescribing of valproate.
- Refer to section 5 'Prescribing valproate' within this policy for safety & educational resources.

5.3 Second specialist signatory requirement – initiation Males & Females

Males: Valproate should not be started in male patients aged under 55 years unless two specialists independently 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.

Females: 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 the Risk Acknowledgment Form that there is no other effective or tolerated treatment and the conditions of the PREVENT (Pregnancy Prevention Programme) are

fulfilled, or there are compelling reasons that the reproductive risks do not apply.

Discontinued /break in treatment: For female patients who have previously been discontinued and/or had a break in treatment, if more than a month has elapsed and valproate is re-started, this will be considered a new initiation; the Risk Acknowledgement Form will have to be completed with a second specialist signatory. This is to ensure compliance with the PREVENT (PPP) is re-checked.

1) **RISK ACKNOWLEDGEMENT FORM** must be completed (separate form: males and females)
2) **A SECOND SPECIALIST SIGNATORY** is required to counter sign Risk Acknowledgment Form.

5.4 Annual review Females

If an existing patient does NOT already have a previous documented Annual Risk Acknowledgement Form that has been signed by two specialists independently, then the risk acknowledgment form MUST be completed with a Second Specialist Signatory.

If the patient already has a documented Annual Risk Acknowledgement Form signed by two specialists independently, then subsequent annual reviews do not require the countersigning signatory unless the patient's circumstances have changed.

5.5 Second specialist signatory Omission – acceptable circumstances

Other than in out of hours situations, as described in subsection 5.12 'Out of hours admissions & valproate prescribing' in this policy, there are a very limited number of scenarios in which valproate can be prescribed despite a second specialist signature not being in place, when one would usually be required. These are:

FEMALES

Patients who have a permanent reason that they do not have the potential to get pregnant (e.g., post-menopausal patients, post hysterectomy, transgender male to female) do not need to complete the Risk Acknowledgement Form beyond Step 1. Step 1 of the form is completed by the specialist prescriber if they consider PREVENT (Pregnancy Prevention Programme) is not needed. Consequently,
the second specialist signatory is not required. This form can be used to support documentation in the medical notes that PREVENT (Pregnancy Prevention Programme) does not apply to this patient.

MALES

If the risk of infertility and the potential risk of testicular toxicity does NOT apply (e.g., the patient is permanently infertile), the Second Specialist Signatory is not required, and the specialist prescriber should use the Risk Acknowledgement Form to document the reason and record in the patients notes.

5.6 Prescribing valproate – second specialist signatory requirements
The Primary prescriber must be a specialist prescriber, as defined in section 3 Definitions.

The Second Specialist Signatory could include the following:

- Consultant adult or paediatric neurologists
- Consultant psychiatrists
- Specialty and associate specialist doctors in psychiatry and neurology
- Specialty doctors in psychiatry
- Paediatrician with special interest in epilepsy
- Paediatrician who regularly managed complex epilepsy or bipolar disorder
- Epilepsy nurse consultant
- Specialist nurses in relevant disciplines/scope of practice
- Specialist pharmacist in relevant disciplines/scope of practice

It is advised that the second signatory for initiation of valproate treatment should not be in direct line management of the primary signatory.

Disagreements:
In cases, where the Second Specialist Signatory disagrees with the primary prescriber, then an opinion from a different Consultant Psychiatrist from another directorate should be obtained. A full review of the patient's circumstances would be needed.

Second Specialist Signatory: prerequisite information
It is the responsibility of the Primary Specialist Prescriber to provide sufficient information for the Second Specialist to reach a decision as to the appropriateness of valproate therapy. Provided information should include:

- Patient demographic details, age, current diagnosis, any relevant co-morbid diagnoses.
- Details of all relevant previous psychotropic therapies prescribed during current and previous episodes of mental illness. Information should include drug, dose, length of time (at relevant dose levels), assessment of response and adverse effects seen.
- If valproate risks are not considered appropriate due to individual fertility circumstances, then these should be clearly stated.
- Concise statement as to why the Primary Prescriber considers valproate to be the only reasonable option for the individual at this point in their care.

Signature:
Ideally the second signature should be completed at the time of prescribing, as a wet ink or electronic signature.

However, the geography of PTHB can often mean that these 2 staff groups may not be working together in person at the time of prescribing, therefore the details of the second signatory can be added to the risk acknowledgement form by the primary specialist prescriber, provided that the second prescriber is identifiable, and in agreement with the decision to prescribe valproate.

In this circumstance:

- The second signatory should be provided with a copy of the Risk Acknowledgment Form.
- There should be a formal, documented agreement from the second signatory that they agree with the decision to prescribe valproate and agrees to add their name to the risk acknowledgement form as a second signatory (e.g. email acknowledgement, temporarily kept on file).
- The risk acknowledgement form is completed with a wet ink or electronic signature by the second signatory within 7 days.
- The completed risk acknowledgement form is added to the patient's notes and uploaded to WCP (inpatient) or WCCIS (outpatient).

5.7 Service users under the care of PTHB
The information contained within this policy, and the required steps outlined, apply equally to those patients attending outpatient appointments. Prescribing of valproate would need to be planned to ensure a Second Specialist Signatory can be consulted before and the necessary steps are completed before valproate is prescribed.

For patients in primary care who have been 'discharged' from the mental health service or are otherwise prescribed valproate for a mental health condition, PTHB community teams MUST accept referrals back into the service for female patients under 55 years who require a yearly review and completion of the Risk Acknowledgement Form. This also applies when a patient highlights a change of circumstance which requires review.

5.8 Risk acknowledgement form
The Risk Acknowledgement Form is used to support and record:

For Females: the clinical reasoning and 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.

For Males: 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).

- Annual Risk Acknowledgement Form For female patients starting valproate and at annual review.

- Risk Acknowledgement form for male patients starting valproate

Once completed, the form should be

- Added to the patient's paper notes
- For inpatients; Uploaded to WCP
- For inpatients; A copy must be sent with the discharge letter to the patient's GP
- For outpatients; A copy should be uploaded to WCCIS and / or WCP as appropriate.
- A copy of the form and the patient guide should be given to the patient or their responsible person

5.9 Pregnancy testing[1]

As with all teratogenic medicines, pregnancy must be excluded before initiation on valproate medicines by a negative plasma pregnancy test, confirmed by a healthcare professional. The aim of pregnancy testing is to provide as much certainty as possible that the service user is not pregnant, before prescribing valproate.

Pregnancy testing relies on detection of human chorionic gonadotropin (hCG), which is released after a fertilised egg has implanted into the uterus wall. Implantation normally occurs 6 to 12 days after ovulation. As hCG will not be released until after implantation, there is a delay between the time of fertilisation of an egg and the time at which a pregnancy is detectable. In the early stages after implantation, an hCG serum assay more sensitively detects pregnancy than an hCG urine dip test. Therefore, if there is any possibility that the patient has recently been sexually active, valproate should not be prescribed until:

- 14 days have elapsed since the last possible day on which the patient could have had unprotected sex (for example, this could be 14 days from the point of admission, or 14 days from the last day on which the patient was given unescorted leave from the ward)
  AND

[1] Clinical manifestations and diagnosis of early pregnancy (medilib.ir)

- A negative hCG serum assay has been obtained after this 14 day period has elapsed.

For patients who have been admitted and who are already prescribed valproate for *mood stabilisation* in the community, if there is any possibility that the patient has recently had unprotected sex, valproate must be **STOPPED**. If still considered clinically appropriate and that the patient can comply with the PPP, the drug can be restarted provided that a negative serum hCG test has been obtained a minimum of 14 days after the last possible day on which the patient could have had unprotected sex.

For patients who have been admitted and who are already prescribed valproate in the community for the treatment of *epilepsy*, if there is any possibility that the patient has recently had unprotected sex, the patient's neurology team must be consulted before stopping the valproate. This consultation should be considered extremely urgent and should occur at the earliest possible opportunity after the patient is admitted. The consultation should involve a thorough discussion about the risks posed by either continuing the valproate or stopping it.

5.10 Contraception advice

All healthcare professionals MUST consult the current guidance as outlined in the valproate Healthcare Professional guide.

The prescriber must ensure the patient is counselled regarding contraception, and that the patient can comply with the need to use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception.

As detailed within PREVENT (Pregnancy Prevention Programme), at least one effective method of contraception, preferably a highly effective user independent form such as an intra-uterine device or implant or two complementary forms of contraception including a barrier method should be used.

Individual circumstances should be evaluated in each case when choosing the contraception method with the patient, involving the patient in the discussion to support her engagement and compliance with the chosen measures. Even if she has amenorrhea, she must follow all the advice on effective contraception.

For patients going into community settings, prescribers MUST ensure effective contraception is prescribed and supplied or effective contraception is

in place before proceeding to prescribe and supply valproate for use in community.

5.10.1 Should the patient become pregnant whilst taking valproate
Female patients should be advised that if they become pregnant whilst taking valproate, they should seek urgent medical advice from their GP or prescriber. The patient should then receive advice from the specialist prescriber within 2 working days (as per RCP PQN standards[2]).

Also refer to the UK Teratology Information Service https://uktis.org/

5.11 Patients who are assessed to lack capacity
For patients who are assessed to lack capacity to consent to treatment or the PPP then prescribing of valproate should be avoided. However, if use of valproate considered to be unavoidable then the following steps will need to be undertaken:

A best interest meeting needs to be arranged for all patients without the capacity to make an informed decision

- Discuss risks of starting valproate treatment with the responsible person. The Risk Acknowledgement Form is used to support and document this discussion.
- For female patients provide the information and advice on highly effective methods of contraception and on the use of valproate during pregnancy to their responsible person and make sure they clearly understand the content.

If, after thorough consideration of the risks, it is concluded that the patient is to be prescribed valproate then:

- a clear risk-minimisation plan should be put in place and clearly documented in the patient's notes.
- The Risk Acknowledgement Form must be completed by two independent specialists (primary prescriber and second specialist signatory)
- The Risk Acknowledgement Form should be used to support and record the prescribing decision and discussion with the patient's responsible person.
- For female patients the conditions of PREVENT (PPP) should be fulfilled or if there are compelling reasons that there is no risk of pregnancy, then this MUST be documented on the Risk Acknowledgement Form.

[22] pqn-community-standards-6th-edition.pdf (rcpsych.ac.uk)

For female patients, the patient's mental capacity needs to be assessed repeatedly to permit discussions with the patient or carer according to the Pregnancy Prevention Programme as soon as her mental state has sufficiently improved. This may not be possible for those patients who permanently lack mental capacity.

5.11.1 Advanced decisions, advanced statements and lasting Power of Attorney (LPA)

Advance Decision (Advance Decision to Refuse Treatment)
If the patient has made a valid and applicable advance decision refusing treatment with valproate then Doctor cannot ignore it unless

(A) Patient has done something inconsistent with the refusal since it was made (such as consented to Valproate treatment covered by the refusal) and even then, had to follow the guidance where needed (ex-asking second specialist signatory where needed)

(B) Valproate treatment is under the MHA—It is important for doctors to respect advance decisions in this context. However, if they need to deviate from this practice clear documentation is needed with compelling reasons supported by bests interests' decision meeting and follow other guidelines. Second opinion Appointed Doctor (SOAD) request should be requested when necessary (ex- after first 3 months of detention for section 3 MHA). In this situation, SOAD should be made aware of a existing Advance Decision as the threshold to certify might be different.
It is important to acknowledge provisions under MHA can only be used if the Valproate indication is to treat mental disorder and not for physical health condition.

Advance statement- If there is an advance statement done by a patient, it should be available to the prescriber. Although Advance statements are NOT legally binding it is important for the prescriber to factor this into the best interest's decision-making process.

Lasting Power of Attorney (LPA) – if decisions concerning the prescription of valproate have been handed over to another person (attorney/donee) under a Lasting Power of Attorney, it is the attorney who
must either consent to or decline the treatment. It is important to check whether there is any
advance decision for refusal to have Valproate is in place when patient had capacity as person with LPA might not be allowed to agree. The same provisions are not legally binding for mental illness if
the individual is admitted to a mental health hospital under the Mental Health Act 1983.

If these are not in place, then the decisions will need to be made by a clinician in the person's best interests, including where someone is detained under MHA

5.12 Out of hours admissions & valproate prescribing

Valproate should not be initiated in a pregnant woman with a mental health disorder detained under the Mental Health Act.

Situations may arise such as the admission of a patient with acute or severe mania outside of normal working hours, where valproate must be prescribed before completing a Risk Acknowledgment Form countersigned by a Second Specialist Signatory is practically feasible.

In such a situation the prescriber is permitted to prescribe valproate, and the following steps should be taken:

- Document in the patient's notes to reflect why valproate has been initiated and the reason a risk acknowledgement form cannot be fully completed at that time.
- The prescriber should document a plan/timeline for obtaining a second signatory for the risk acknowledgement form. The second signatory should be obtained within 7 days of initiating valproate.
- Before a patient is discharged or granted short term leave a current Risk Acknowledgement Form must be fully completed.

The above steps apply only if initiating valproate out of hours.

If a patient is admitted out of hours who is already prescribed valproate, the prescriber can continue this valproate prescription. It is likely that existing patients would have a current risk acknowledgement form. This should be located and added to the patients notes.

5.13 Specific patient groups

5.13.1 Females under 55 years: permanent absence of pregnancy risk, e.g. post-menopausal or post-hysterectomy

Patients who have a permanent reason that they do not have the potential to get pregnant (e.g., post-menopausal patients, post hysterectomy, transgender male to female) do not need to complete the Risk Acknowledgement Form beyond Step 1 and consequently the second specialist signatory is not required. The Risk Acknowledgment Form can be used to support documentation in the medical notes that PREVENT (Pregnancy Prevention Programme) does not apply to this patient.

It is the responsibility of the clinical team/specialist to definitively confirm a diagnosis of 'post menopause' and document this clearly within the patient's

notes, and on Step 1 of the risk acknowledgement form. It should not be assumed that the patient has reached post menopause based solely on age, due to individual variation. It is important to bear in mind women can experience menopausal symptoms with irregular periods during the peri-menopausal stage, which can last several years. There is still a risk of pregnancy during the perimenopausal stage.

Please access the most up to date guidelines for reference on Menopause Nice guidance: Menopause: diagnosis and management

5.13.2 Males – risk of infertility and testicular toxicity not applicable, e.g. permanent infertility

If the risk of infertility and the potential risk of testicular toxicity does NOT apply (e.g., the patient is permanently infertile), the second specialist signatory is not required, and the specialist prescriber should use risk acknowledgement form to document the reason and record in the patients notes.

5.13.3 Pre-Menarche

Female children who have not yet reached menarche (not started her periods) DO NOT need to fulfil the conditions of PREVENT (Pregnancy Prevention Programme), but they and their responsible person need to be aware of the risks for the future. The patient / responsible person should be provided with a copy of the Patient guide and the patient / responsible person reminded to contact their GP once the female child using valproate experiences their first period.

Their GP MUST refer the patient back to the specialist prescriber. The Risk Acknowledgment Form can be used to support documentation in the medical notes that PREVENT (Pregnancy Prevention Programme) does not apply to this patient. Only Step 1 of the Risk Acknowledgement Form needs to be completed at this stage and a Second Specialist Signatory is not required.

The form MUST still be completed annually and when the patient reaches menarche, the Risk Acknowledgment Form must be completed fully with a Second Specialist Signatory and the compliance with Pregnancy Prevention Programme will be mandatory.

5.13.4 Transgender and Non-binary people

A transgender individual is someone whose gender identity is not congruent with the sex they were assigned at birth. A transgender woman is someone who was assigned the sex of male but is a woman. A transgender man is someone who was assigned the sex of female but is a man. The term transgender is often shortened to 'trans'. The term non-binary describes any gender identity which does not fit the male and female binary.

Currently there is no specific advice available from the MHRA with regards to valproate prescribing within this cohort of patients, although there are challenges associated. The appropriate pathway for individual prescribing decisions (male v female) will depend upon the biological sex assigned at birth and the stage of medical gender transition that has been reached.

Patients who identify as a man but have an intact uterus should be treated as female for the purposes of pregnancy prevention. Patients who identify as a woman but have the ability to father a child should be treated as male for the purposes of pregnancy prevention.

Prescribers will be required to have individual discussions with patients who have transitioned or are transitioning, or who are non-binary. It is important that prescribers have these discussions, ensuring they respect the patient's gender identity and their autonomy to make decisions about their own healthcare. For example, using the correct name and pronouns. In addition, it may be a difficult experience for those who have transitioned or are transitioning; additional empathy and compassion may be required.

Further resources for prescribers are available in appendix 1.

5.13.5 Process for people who disengage from MH services

5.13.5.1 Males who disengage from specialist services

Once a male has been commenced on valproate by a specialist prescriber, ongoing prescribing is undertaken by GP. There is no requirement for annual review of valproate treatment unless the patient's circumstances change and require further review / specialist input.

5.13.5.2 Females who disengage from specialist services

Once a female for whom PPP applies has been commenced on valproate, the need for ongoing valproate prescription *must* be reviewed annually, using the ARAF, by the specialist prescriber.

Where a patient does not attend for review, the patient should be sent a further appointment. The appointment letters must make the purpose of the appointment clear (i.e. to review valproate prescribing and to enable the ongoing prescription of valproate by the GP for the next year) An example can be found in appendix B & C.

Following two unattended appointments, the team should contact GP to ensure that the patient's details are correct. The patient should then be contacted via phone and/or email and a further letter sent outlining the risks of non-attendance i.e., that valproate prescription will be discontinued if they do not attend.

Consideration should be given to the mode of appointment, i.e., face-to-face, videoconferencing, phone call (NB PPP documentation does not require 'wet' signature and can be completed virtually if appropriate.)

Following three non-attendances and reasonable attempts to contact the patient, the GP and specialist prescriber must agree an explicit plan to continue to attempt to engage the patient, and/or consider whether valproate prescription is still indicated. This plan must be informed by potential benefits and risks to the patient and may ultimately include withdrawal of valproate. In the latter scenario, the patient must be informed of decision making and rationale by letter. The letter must include advice as to how to access services if their condition deteriorates and/or if they disagree with the decision.

This whole process of non-attendance and lack of review completion should ideally be reviewed and completed in a 90-day period.

5.13.6 People moving to the area

Males aged 55 and under moving into the area who are prescribed valproate do not require further review by mental health services for the sole purpose of ongoing valproate prescription. GPs can continue to prescribe as with any other drug.

Females for whom PPP applies should have an ARAF in place which should be on the GP record. If there is no ARAF or one cannot be located, and where the indication for prescribing is mental health, the female should be referred by GP to the mental health service for urgent review. The Specialist Prescriber should consider the clinical indication and act in accordance to the Healthcare Professional guide

Where a female has an ARAF, the GP should refer to the relevant Community Mental Health Team (CMHT) to ensure that ongoing annual review is facilitated. The existing ARAF should be sent from GP to the CMHT as part of the referral.

5.14 Clinical Pharmacist screening and authorisation of supply

PTHB MH wards currently have very limited pharmacy input, therefore cannot provide a full clinical screening process.

It is anticipated that the majority of valproate prescribing will be seen on Felindre acute Mental Health ward, but all clinical Pharmacists must be familiar with the Healthcare Professional guide which clearly outlines their roles and responsibilities.

Some formulations of valproate are kept as a stock medicine on PTHB MH wards. In the absence of pharmacy input, MH ward staff are responsible for

the ordering and management of stock on their wards, in line with agreed stocklists. Other formulations of valproate that are non-stock items can be ordered from the supplying pharmacy on a named patient basis.

As part of their clinical check, Pharmacy professional must check that the patient has a current Risk Acknowledgment Form completed. If the form has not been completed, the clinical team/prescriber should be contacted to complete the form as soon as possible.

Exceptions to this would include any prescribing that has occurred out of hours, as detailed in section 5.12 Out of hours admissions & valproate prescribing. In such this circumstance, the pharmacy professional should

- check the clinical team have documented this out of hours use on the patient's record.
- The pharmacy professional should also document on the patient's record the out of hours use and requirement for second signatory.
- The MDT must ensure completion of the RAF within 7 days. Under no circumstances should a patient be discharged without a RAF having been satisfactorily completed.

If there are issues with non-compliance in completing the Risk Acknowledgment Form as per policy then a Datix report should be submitted, and highlighted to the medicine safety officer via powys.mso@wales.nhs.uk

5.15 PTHB Hospital Use of valproate containing medicines

Inpatient named medicines are supplied from Nevill Hall Hospital (South & Mid Powys) and Bronglais Hospital (North Powys). Inpatient named supply can be obtained by emailing the supplying pharmacy the request for non-stock medicine and if no PTHB Pharmacist clinical check attaching a copy of the patient's medicine chart. TTOs can be obtained from the supplying pharmacy by scanning and emailing the TTO document and if no PTHB Pharmacist clinical check a copy of the patient's medicine chart.

Patients may also bring their own supply with them onto the ward, supplied by their community pharmacy or dispensing practice.
PTHB Pharmacy team may also dispense and relabel medication at ward level.

PTHB expect that all suppliers adhere to valproate supply requirements; providing a patient information leaflet, patient safety card and warning sticker on the medication box.

Regulation states that from 11th October 2023, valproate-containing medicines must be dispensed in the manufacturer's original full pack. This legislative change has been made to ensure that patients always receive specific safety warnings and pictograms, including a patient card and the

Patient Information Leaflet, which are contained in the manufacturer's original full pack. These materials form a key part of the safety messaging and alert patients to the risks to the unborn baby if valproate-containing medicines are used in pregnancy.

5.15.1 In patient medication

Supply during inpatient stay must be in original packaging. However, it is the responsibility of the Clinician and Pharmacy team to ensure that correct supply has been authorised at the point of discharge (see information below).

5.15.2 Short term leave medication

Medication for short term leave may be requested from Nevill Hall or Bronglais Hospital, operating as the supplying Pharmacy. If this is not achievable, due to timescales involved, then this can be supplied using WP10(H) prescriptions; dispensed at a community pharmacy.

Valproate should be dispensed in original packs for short term leave unless there are concerns about the appropriateness of this for the patient, as detailed in 5.15.4 Exceptional circumstances: non original pack dispensing. The patient must be requested to return their short-term leave medication with them when they return to the ward, where it can be used during their inpatient stay or to support further home leave.

If in exceptional circumstances original packs are not used the supplying pharmacy, PTHB Pharmacy Team or community pharmacy must ensure that the following are supplied, regardless of patient gender.

- Patient Information Leaflets (PILs)
- Valproate Warning stickers with a pictogram (figure 1)
- MHRA valproate patient card

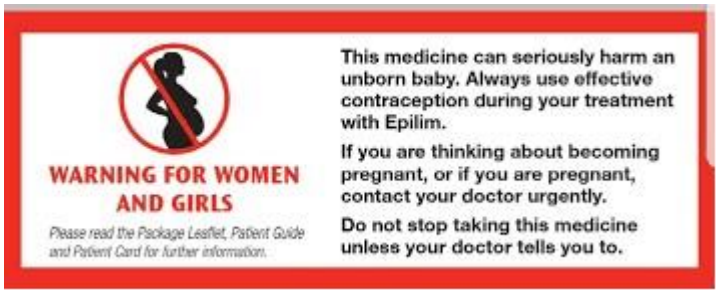


Figure 1 valproate warning sticker with pictogram

5.15.3 Discharge medication

Discharge Medication must be supplied in the manufacturer's original pack, unless there are exceptional circumstances. Ward based Pharmacy teams must be aware of this requirement when supplying TTOs, either prepared by supplying pharmacy or utilising PODs for discharge.

Medication for TTOs may be requested from Nevill Hall or Bronglais Hospital, operating as the supplying Pharmacy. WP10(H) prescriptions should only be

used for TTOs where timescales do not allow to obtain a supply from supplying pharmacy, or the patient requires a compliance aid such as a monitored dosage system or medication administration record (MAR) chart prepared by the community pharmacy.

5.15.4 Exceptional circumstances: Non-Original Pack Dispensing
There may be exceptional circumstances where original full pack dispensing is not appropriate, and the prescriber may wish to deviate from original full pack dispensing. For Example:

- Risk to Self-Harm Suicide
- Monitored dosage systems (MDS)

In circumstances where there is a risk in supplying a full pack, a reduced quantity may be supplied, which will not be supplied in original packaging, and must adhere to the standards set out in 5.15.2 Short term leave medication.
Community pharmacies willing to supply valproate in a MDS must ensure that patient information leaflets and MHRA valproate patient safety card are supplied, and warning stickers are placed appropriately onto the MDS tray.

The Pharmacy poster provides important actions for pharmacists and dispensing valproate to female patients.

5.16 Incident reporting
Any errors associated with valproate prescribing, supply or administration must be reported via Datix. This includes instances where the Risk Acknowledgement Form has not been completed correctly and medication is supplied without completion of the form in line with this policy.
Incidents associated with incompletion of the Risk Acknowledgement Form should be assigned to the clinical director of that service. The MSO must also be informed of any incidents regarding valproate via email at powys.mso@wales.nhs.uk and will discuss issues raised within MSG meetings.

Prescribers should be aware that valproate is subject to 'black triangle' reporting via the Yellow Card scheme. For medicines showing the black triangle symbol, the MHRA asks that **all** suspected reactions (including those considered not to be serious) are reported through the Yellow Card scheme. An adverse reaction should be reported even if it is not certain that the drug has caused it, or if the reaction is well recognised, or if other drugs have been given at the same time. Reports can be made by health care professionals or the patient themselves here Reporting side effects of medicines and vaccines - All Wales Therapeutics and Toxicology Centre (nhs.wales)

	5.17 Training Upon ratification, this policy will be circulated appropriate stakeholders within PTHB. Whilst no specific training is required, a number of awareness sessions will be offered via the division service. This may be virtually via MS Teams or directly by attending team meetings. The policy will also be shared with relevant stakeholders within PTHB.

6 Monitoring Compliance, Audit & Review

This document will be reviewed every three years or earlier should audit results, changes to legislation or practice indicate otherwise.

Annual audit will be undertaken of several patients initiated on valproate by a PTHB prescriber to ensure that all relevant steps within this policy have been followed.

7 References

Sodium Valproate resources and information - Powys Teaching Health Board (nhs.wales)

National Patient Safety Alert: Valproate: organisations to prepare for new regulatory measures for oversight of prescribing to new patients and existing female patients (NatPSA/2023/013/MHRA) - GOV.UK (www.gov.uk) Published 28 November 2023

https://www.gov.uk/drug-safety-update/valproate-re-analysis-of-study-on-risks-in-children-of-men-taking-valproate#re-analysis-of-study-examining-risk-in-children-of-men-taking-valproate Published 30 August 2023

Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): new safety and educational materials to support regulatory measures in men and women under 55 years of age - GOV.UK (www.gov.uk) Published 22 January 2024

Valproate-report-review-and-expert-advice.pdf (publishing.service.gov.uk) Medicines and Healthcare products Regulatory Agency November 2023

1. bpeg open uk rcpch documenton prescribing valproate 020124 final 1.pdf 31 January 2024

2. february2024 prescribing valproate to female patients under 18 years of age.pdf (rcpch.ac.uk) Update 31 January 2024

ps04_18.pdf (rcpsych.ac.uk) December 2018

Valproate use in men: as a precaution, men and their partners should use effective contraception - GOV.UK (www.gov.uk) September 2024

Appendix A – further resources available for prescribing valproate in Transgender and Non-binary people

Sexual the FSRH CEU Statement: Contraceptive Choices and Sexual Health for Transgender and Non-Binary People, The Faculty of Sexual and Reproductive Healthcare (FSRH) of the Royal College of Obstetricians Gynaecologists, Clinical Effectiveness Unit (CEU), Last Published 1st October 2017.
contraceptive-choices-and-sexual-health-for-transgender-non-binary-people-oct-2017.pdf

Inclusive care of trans and non-binary patients, BMA, British Medical Association.
https://www.bma.org.uk/advice-and-support/equality-and-diversity-guidance/lgbtplus-equality-in-medicine/inclusive-care-of-trans-and-non-binary-patients

Welsh Government LGBTQ action plan
LGBTQ Action Plan English purple and green (gov.wales)

Royal College of Nursing Fair care for trans and non-binary people
Fair Care for Trans and Non-binary People| Royal College of Nursing (rcn.org.uk)

Appendix B - suggested format for invitation appointment letter for annual review

Dear [name of patient]

Annual review of Valproate prescription

As you know, you are prescribed a medication called valproate (the brand name might be Sodium Valproate, Epilim, Depakote, Convulex, Episenta, Epival or others).

To continue to receive prescriptions of valproate, you must attend for annual review with a specialist prescriber. This is because although this medication is very effective for your symptoms, there is a known risk to the development of babies where the mother takes valproate.

The purpose of the appointment is to review your mental health, ensure that you still require this medication and to complete the Annual Risk Acknowledgement Form (ARAF) with you which is required for your GP to continue to issue prescriptions.

More information can be found here: Medicines and Healthcare products Regulatory Agency (filecamp.com)

Please be in touch with the [name] medical secretary to arrange an appointment.

Appointments can be in person at [name of venue], by videocall or by telephone.

If we do not hear from you, we will contact you again.

Please be advised that we cannot recommend that your GP continues to prescribe this medication without annual review. If we do not hear from you, your prescription is likely to be stopped.

Yours sincerely

[Name]

On behalf of Dr [name]
Consultant Psychiatrist

Appendix C – easy read letter

Dear [name of patient]

Appointment

As you know, you take a medication called valproate (the brand name might be Sodium Valproate, Epilim, Depakote, Convulex, Episenta, Epival or others).

You need to see Dr [name] to make sure that you can keep having this medication. This is because we know that if people who take this medication become pregnant, it can harm the baby.

Dr [name] will make sure that this is still the right medication for you. If it is, they will fill in a form with you, to make sure you can still have the medication.

More information can be found here:

Please be in touch with the [name] medical secretary to arrange an appointment

OR

An appointment has been made for you to see Dr [name]

On [date]
At [time]
At [place]

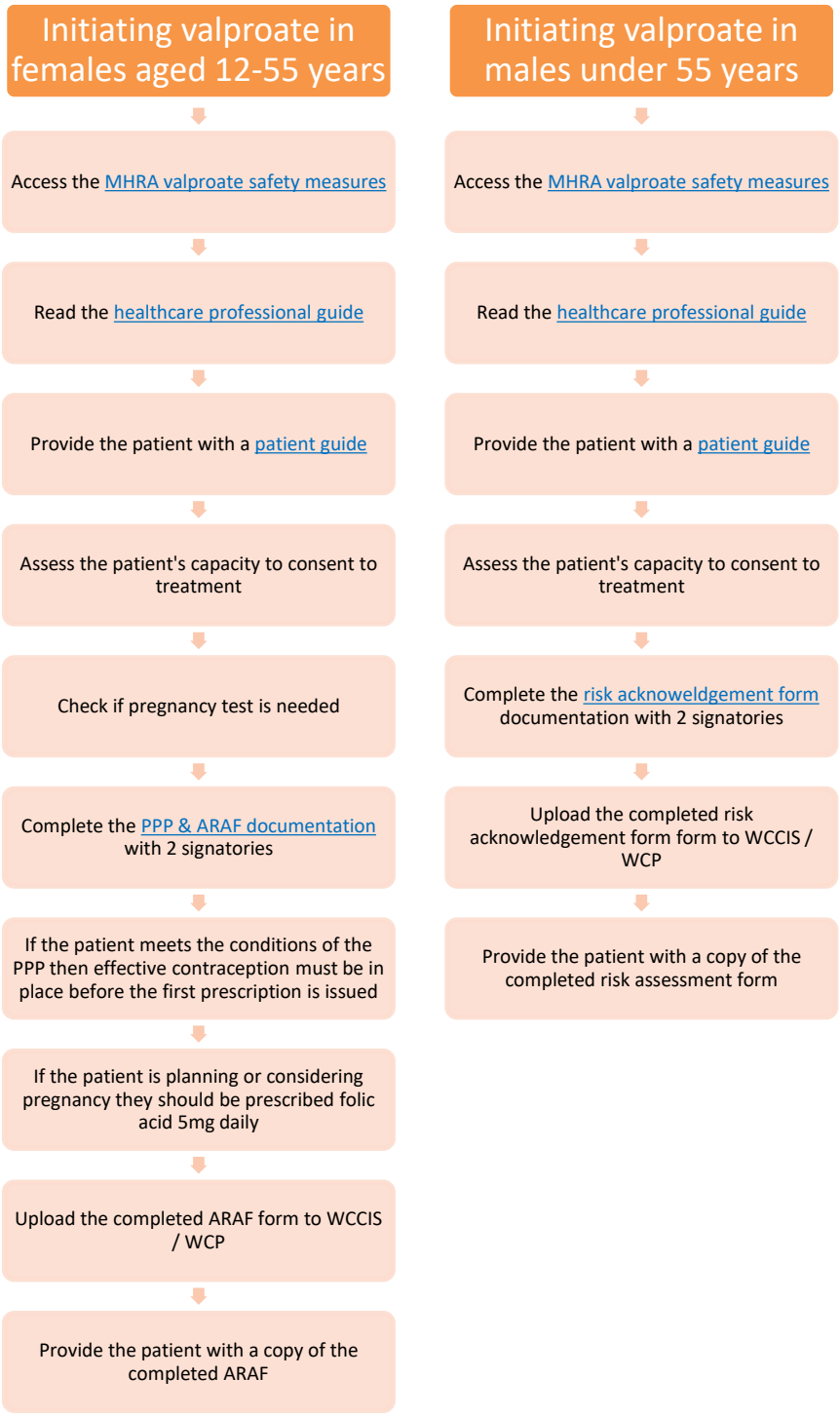
If you can't come to this appointment, please ring [name of med sec] to make another appointment.

Your doctor cannot keep giving you this medication unless you have an appointment.

Yours sincerely

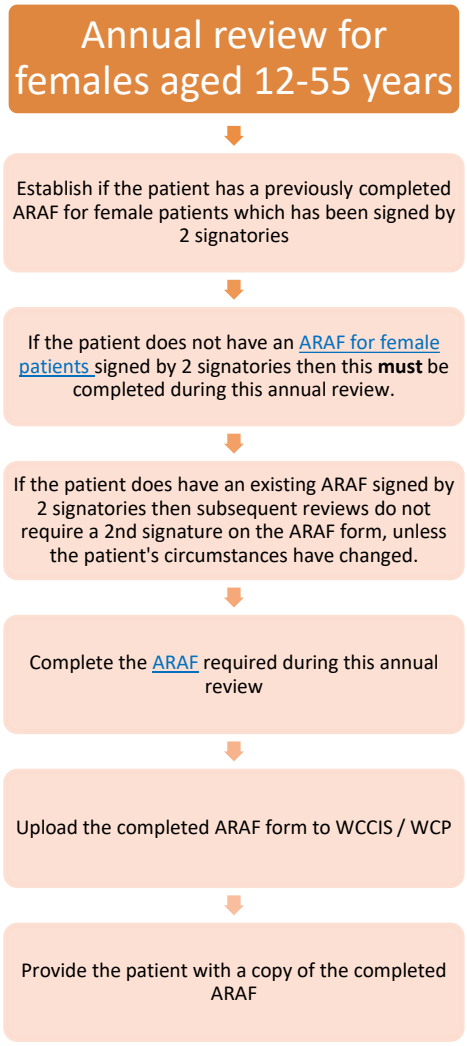
[Name]
On behalf of Dr [name]
Consultant Psychiatrist

Appendix D – flowchart for initiating valproate



PPP – pregnancy prevention plan
ARAF – annual risk acknowledgement form
WCCIS – Welsh Community Care Information System
WCP – Welsh Clinical portal

Appendix E – flowchart for annual review for females aged 12-55



PPP – pregnancy prevention plan
ARAF – annual risk acknowledgement form
WCCIS – Welsh Community Care Information System
WCP – Welsh Clinical portal