Safe prescribing of valproate – Frequently Asked Questions for Primary Care and Community Pharmacy Teams

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About this guidance

This guidance has been developed by the local Valproate Safety and Implementation Group consisting of the following stakeholders from the local healthcare system: Consultant Neurologists and Psychiatrists for Adults and Paediatrics, Specialist Nurses for Epilepsy, General Practitioners, Specialist Pharmacists and Pharmacy Technicians including representation from local Sexual Health Services.

Purpose

To provide clinical advice to clinicians for frequently asked questions (FAQs) on the safe prescribing of valproate for patients under 55 years of age. These FAQs should be read in conjunction with the Valproate pathway and guidance.

All practitioners treating people taking valproate should be mindful that some individuals who do not identify as female may be of childbearing potential therefore patient groups have been defined as follows within this local guidance:

- **Group 1 - Girls, women, trans men and non-binary people of childbearing potential (i.e. potential to fall pregnant) under 55 years of age**
- **Group 2 – Boys, men, trans women and non-binary people not of childbearing potential aged under 55 years old.**

Frequently Asked Questions

Prescribing valproate safely

What does 'no other treatment is effective or has been tolerated' mean?

The ARAF and RAF state 'patient's condition has not responded to other treatments or other treatments are not tolerated'. This does do not mean that the patient needs to have tried all other treatments for their condition before using valproate. Individual decision between clinicians and patient, taking account of condition and reproductive risks will be undertaken. Valproate may remain first line treatment for some epilepsy syndromes, where risk of delayed treatment is significant.

Many patients have been commenced on valproate as first line treatment before MHRA changed guidance in 2017/2018. For some patients, stopping valproate comes with risk of condition destabilisation leading to an increase in mortality and morbidity. For patients with epilepsy who can drive, the current Driver and Vehicle Licensing Agency (DVLA) guidance requires the patient to stop driving if switching to alternative potentially less effective anti-seizure medication, which can have a huge impact quality of life and ability to work. Many patients will decline to cease valproate treatment therefore the patient's individual risks of starting, continuing or ceasing treatment need to be carefully considered.

Who can prescribe valproate?

In line with local guidance, primary care clinicians can initiate valproate on the advice of a specialist with a completed ARAF or RAF.

What about when valproate is used for unlicensed indications?

Recognised unlicensed indications for valproate use include headache conditions (migraine and cluster) and psychiatric indications in those with chronic neurological conditions (such as Huntingdon's disease). The patient should have tried all other reasonable options for treatment taking account tolerability, comorbidities and contraindications and must be 'no' or 'low' risk categories of reproductive risks for valproate to be considered (see Table 1).

Documenting consultations

How can I document my consultations?

Robust documentation and read codes are vital following patient consultations. Where Ardens templates are available, the use of 'Valproate Monitoring' template is strongly recommended.

Contraception

What contraceptive options are available for group 1 patients of childbearing potential taking valproate?

Long-acting reversible contraceptives (LARC) preferred and recommended; however this is **not mandated** (see Guide for Healthcare Professionals). Group 1 patients on valproate should not be denied valproate if they do not opt for a LARC. Group 1 patients on user dependent hormonal contraception must be advised to use two complimentary contraceptive methods.

What should we do if we identify that a group 1 patient of childbearing potential does not have contraception in place?

Where a patient has been identified as not having contraception in place, the patient should be invited urgently for a further consultation on contraceptive options, and where necessary referred to the sexual health clinic or an appointment made with the practice nurse where LARC is available.

What should we do if a group 1 patient of childbearing potential declines contraception?

If a patient of childbearing potential in Group 1 declines contraception, their individual reproductive risk should be assessed, taking into account their personal circumstances, medical history, and any previous unplanned pregnancies (including those that occurred while using valproate without contraception).

No patient should be removed from valproate against their will, nor should treatment be withdrawn solely because they decline contraception.

Clinicians must ensure the patient has received comprehensive counselling about the reproductive risks of continuing valproate without reliable contraception. This counselling should be delivered in a supportive, non-directive manner that respects the patient's reproductive autonomy, including the choice not to use contraception when they are not actively trying to conceive.

A detailed record of the discussion—including the information provided, the patient's decision, and the clinical rationale—should be documented in the patient's clinical notes.

Pregnancy Prevention Programme Exemptions

What is included as an exemption from the PPP (PREVENT)?

Exemptions from the Pregnancy Prevention Programme apply only when there is no possibility of pregnancy or when a person cannot consent to sexual activity that could lead to pregnancy. Examples of exemptions include the permanent absence of risk from pregnancy due to hysterectomy, oophorectomy (not seeking fertility treatment), post-

menopausal/primary ovarian failure, partner infertility or vasectomy, significant learning disability or cognitive impairment, where the person cannot understand or consent to sexual relationships, therefore pregnancy risk is absent. The Mental Capacity Act (MCA) 2005 provides useful guidance for professionals when making this decision.

Other situations in which the PPP (PREVENT) may not apply—though the patient should still have an annual review in case circumstances change—include:

- Sexual relationships that cannot result in pregnancy (and where the individual is not seeking fertility treatment).
- Individuals who are not in a sexual relationship for religious, social, or personal reasons.
- Patients who have not yet reached menarche.

Pregnancy and family planning

What should I do if a group 1 patient wishes to stop contraception to actively conceive?

Valproate for epilepsy:

MHRA guidance acknowledges that there may be patients who may still conceive on valproate for epilepsy, if two specialist agree that other treatments have not been effective or tolerated for their condition.

The patient needs urgent review by GP to ensure they have been informed of reproductive risks, commenced on folic acid 5mg a day and an urgent referral made to their specialist (within days) for discussion on valproate related reproductive risks, and benefits versus risks of ongoing valproate treatment if planning a pregnancy. The patient should be advised **to continue contraception and not to stop valproate treatment** until reviewed by the specialist.

If the specialist and patient decide risks of withdrawal of valproate to the mother are greater than reproductive risks to the fetus on valproate, valproate should continue to be prescribed. The patient should not be denied usual NHS care including withholding of valproate in Primary Care, or sanctioned for their decision to conceive on valproate. **No patient should be taken off valproate without their consent.**

Valproate for bipolar disease:

Valproate is contra-indicated in pregnancy for the treatment of bipolar disease. The patient needs urgent review by GP to ensure they have been informed of reproductive risks, commenced on folic acid 5mg a day and an urgent referral made to their specialist (within days) to consider withdrawal of valproate to switch to an alternative treatment if applicable.

What should I do if a group 1 patient is pregnant?

For those not under specialist care see below under ‘Referral’.

The patient needs urgent review by GP to ensure they have been informed of reproductive risks and commenced on folic acid 5mg a day.
When a patient is under already specialist care, inform the specialist service immediately. All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine at their local Maternal Medicine Hub (Addenbrookes Hospital for C&P).

If valproate is to be continued through pregnancy for epilepsy, ongoing prescriptions will be provided to the patient for the duration of pregnancy directly by the specialist service. The specialist should discuss mitigation of reproductive risks (eg considering lowest effective dose which could be in combination with other less teratogenic antiseizure medications, using prolonged release preparations, and dividing the daily dose into several smaller doses throughout the day).

Valproate is contra-indicated in pregnancy for the treatment of bipolar disorder. If pregnancy is confirmed, urgent discussion should take with the specialist who will review the patient as soon as possible to discuss treatment options.

What should I do if a Group 2 patient wishes to conceive?

For group 2 patients prescribed valproate who wish to start a family within the next 12 months, they should be referred urgently to their specialist. This is due to potential risks of valproate affecting fertility and risk of neurodevelopmental conditions in the child. The patient should be reminded not to stop their valproate treatment and to continue using contraception until advice from the specialist is sought.

Referrals

Who needs referral to specialist services?

a. All Group 1 patients who are prescribed valproate but are not already under specialist care (unless an ARAF specifies a permanent exemption from PREVENT).
b. Group 2 patients who wish to conceive a child within the next 12 months.
c. Group 2 patients who wish to consider change in treatment from valproate to another medication

How should primary care prioritise patients for referral?

Please see Table 1 below for priority for referral based upon reproductive risk assessment.

Those patients in Group 1 who are pregnant and taking valproate must be prioritised for specialist referral (immediately) for discussion of the benefits versus risks of ongoing valproate treatment during pregnancy. These patients need urgent review by GP to ensure they have been informed of reproductive risks, started on folic acid 5mg a day (in first trimester) before referral.

Those Group 1 patients who are actively trying to conceive, need urgent review by GP to ensure they have been informed of reproductive risks, commenced on folic acid 5mg a day and an urgent referral made to their specialist (within days) for discussion on valproate related reproductive risks, and benefits versus risks of ongoing valproate treatment.

All other Group 1 patients not under specialist care who require an ARAF, a routine referral should be made.

Table 1 - Priority for referral based upon reproductive risk assessment

Reproductive risk assessment	**Group 1 patients**	**Priority for referral**	**Group 2 patients**	**Priority for referral**
High risk	• No contraception and sexually active • Actively trying to conceive	**Urgent**	Actively trying to conceive	**Urgent**
Moderate risk	• Barrier methods	Routine	• Barrier Methods	N/A
Low -Moderate risk	• User dependent hormonal contraception	Routine		N/A
Low risk	• LARC prescribed • Patients in a sexual relationship which could not result in pregnancy (eg same sex relationships or established male partner with vasectomy) • Not in a sexual relationship on religious or social grounds	Routine	.	N/A
No risk	• Hysterectomy • Bilateral oophorectomy • Post-menopausal • Infertility from another cause (not seeking fertility treatment)	Only needs referral if ARAF for exemption has not been completed.	• Male vasectomy • Infertility from another cause	N/A

Specialist will follow the above table for referral triage and prioritisation.

What do I do if my patient has a previous ARAF that is over 12 months old?

Patients who are under secondary care and have had a review and a completed ARAF within the past 15 months **will not** need a referral as they should have a planned annual review where the ARAF form will be completed by two specialists.

If an ARAF has been completed however, is over 15 months old, please send advice and guidance to specialist team to ensure that a review is planned.

Do I need to refer Group 1 patients who have already had an ARAF stating a permanent reason that pregnancy cannot occur, and so are not under annual review of ARAF?

No. Please see below question on PPP exemptions for further information regarding permanent exemptions to the PPP.

Group 1 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 have the ARAF completed beyond step 1 and do not need an ARAF to be completed by two independent specialists. This form can be used to support documentation in the medical notes that prevent does not apply to this patient.

My patient was prescribed valproate by paediatric services but is no longer under their care. Who should I refer to?

For those aged 18 and over **and** no longer under paediatric services, refer to the respective adult services.

What can the practice do to support the referral? See referral form

Where it has been identified a referral to a specialist is required, the practice should discuss this with patients. Patients should be given an appointment with a clinician with appropriate expertise to have this discussion. Patients should be informed of the reproductive risks of valproate, offered appropriate contraception and the need to refer to a specialist.

Practice must ensure that the referral form available in the GP clinical system is completed in full to support in secondary care triage of referrals received and to ensure that the most up-to-date and accurate patient information is available for the specialist to review the risks/benefits of continuing valproate. The purpose of the referral is not just an administrative task to complete an ARAF. The purpose of completing a Valproate ARAF with the patient is to record that continuing on valproate is still appropriate, and reproductive risk mitigation strategies are in place.

My patient is refusing referral to secondary care, what should I do?

Valproate is unlicensed for patients under the age of 55 with childbearing potential if the conditions of the Pregnancy Prevention Programme (PREVENT) (PPP) are not met. Patients should be strongly encouraged to attend appointments with the specialists to ensure they are receiving appropriate care. If the patient still does not engage with the referral, you should

urgently discuss with the patient's specialist so that a management plan can be agreed for the individual patient. It may be that contact needs to be made by both the patient's specialist and the patient's GP practice, on multiple occasions, to support in patient engagement with services.

How should I manage a patient who had valproate initiated by primary care?

For patients where valproate was initiated in primary care for clinical indications, a new referral will be required to secondary care depending on the clinical indication for use.

My patient is prescribed valproate for an indication other than epilepsy or bipolar which was initiated by secondary care, how should this be managed?

These patients should be referred to the clinician / clinic who commenced treatment.

Risk Acknowledgment Forms

Are GP practices able to complete the ARAF?

Some surgeries have asked whether they can complete any incomplete or out of date ARAFs. The Medicines and Healthcare products Regulatory Agency (MHRA) update specifically states these must be completed by the specialist and countersigned by an appropriate secondary signature with relevant expertise. The ICB would not encourage the completion of ARAFs in primary care.

There may be General Practitioners with Extended Roles who are working and would be able to countersign an Annual Risk Acknowledgement Form.

Where it has been identified that a patient does not have an ARAF completed within the last 15 months, this may be documented in the patient clinical records to acknowledge the missing documentation, and action taken to rectify.

My patient is currently exempt from the Pregnancy Prevention Programme, do they need an updated ARAF?

Group 1 patients with a permanent exemption from the Pregnancy Prevention Programme do not need an updated ARAF and do not need to have an annual review of ARAF.

The latest MHRA alert mentions group 2 patients (boys, men, trans women and non-binary people not of childbearing potential) aged under 55 years old, do I need to do anything about this group of patients?

New initiations of valproate: The alert requires that any group 2 patient under the age of 55 years **newly initiated** on valproate must have a Risk Assessment Form (RAF) completed by two specialists. This is a one-off form and does not need to be completed annually. On receiving the form, this must be uploaded into the patient's clinical record and recoded using the read codes above.

The ICB also strongly suggests adding a script note to valproate prescriptions on the repeat template with the date the RAF was signed so it is easily identifiable that this has been completed.

In the event a group 2 patient under the age of 55 years is newly started on valproate and has not received a RAF, contact the initiating specialist via advice and guidance to request the RAF to be completed.

Existing valproate users: A RAF is not required. The MHRA has issued precautionary advice for them and their partners to use contraception due to a possible small increased risk of neurodevelopmental conditions in children conceived whilst taking valproate. Review by two specialists is not required for group 2 patients already taking valproate.

Group 2 patients should be given the precautionary advice at their next routine review. If a patient expresses plans to start a family within the next 12 months, the patient should be referred urgently to the specialist for advice. If a patient wishes to discuss a change in treatment, the patient should be referred on a routine basis to the specialist for advice. **The patient must be reminded not to stop valproate treatment before consultation with the specialist.**

My patient has been reviewed by secondary care, what steps do I need to take?

Once the ARAF or RAF has been received, this should be uploaded into the patient's clinical record and recoded as per the recodes highlighted within the Valproate pathway and guidance. It is also suggested that the date the ARAF or RAF was completed is added to all valproate repeat templates as a script note so it is quickly visible when prescriptions are requested. Where the patient is exempt from the PPP (PREVENT) this must also be appropriately read coded, and added to the valproate repeat templates for future reference.

For group 1 patients of childbearing potential there must be an annual discussion in primary care, of the risks of valproate use in pregnancy to ensure the patient understands the need to use effective contraception, review of contraception options if applicable, where clinically appropriate and the need for the annual review by their specialist (unless exempt from PPP).

Group 2 patients under the age of 55 years should be given the precautionary advice for them and their partners to use contraception regularly.

Where Ardens is available, the 'Valproate monitoring' template should be used. The patient should be reminded never to stop treatment without advice from the specialist and what to do if the patient becomes pregnant or wishes to start a family.

Advice for General Practice

What ongoing actions does the practice need to undertake to ensure we are compliant with the alert monitoring?

CQC may request evidence from the practice for assurances that this alert has been actioned and continues to be managed to ensure the safety of patients. Practices 'must do all that is reasonably practicable to mitigate risks'.

It is strongly suggested that searches are run monthly to ensure all patients meet the requirements of the alert. Where requirements are not met, the practice must act, i.e. discuss reproductive risks, advise on contraception and refer to specialist services to consider if ongoing prescribing of valproate is indicated. This process must be documented and accessible to staff responsible for overseeing this process.

The practice should have a robust recall system in place to ensure patients prescribed valproate are offered an annual medication review in primary care.

Who can I contact for further advice or to raise an issue?

If you have any questions, concerns or need advice regarding this alert, please contact the Integrated Care Board Medicines Optimisation Team.

What should happen if patient declines to engage with review and monitoring?

The patient's GP and Specialist should attempt to contact patient and explain the need for review and provide the patient information guide. If concerns remain, there should be an open dialogue between the primary care clinician and the patient's specialist to facilitate an action plan to support in review of and attendance by the patient at appointments.

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