



Frimley Health ICS Medicines Board.

Shared care protocol: Valproate for people of childbearing potential aged under 55.

(The term valproate refers to medicines containing sodium valproate, valproic acid or semi sodium valproate)

Agreed by NHS Frimley Medicines Optimisation Group	November 2024
Ratified by NHS Frimley Medicines Board	November 2024
Review date	November 2026

The content of this shared care protocol was correct as of October 2024. As well as these protocols, please ensure that [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [Medicines and Healthcare products Regulatory Agency](#) (MHRA) or [NICE](#) websites are reviewed for up-to-date information on any medicine. Where patient is stated please substitute parent/ carer/ legal power of attorney as appropriate.

### Specialist responsibilities

- Assess the patient and provide diagnosis; ensure that this diagnosis is within scope of this shared care protocol ([section 2](#)) and communicated to primary care.
- Use a shared decision-making approach; discuss the benefits and risks of the treatment with the patient and provide the appropriate counselling (see [section 11](#)) to enable the patient to reach an informed decision. Provide an appropriate patient information leaflet. Resources to support appropriate information include [www.medicinesforchildren.org.uk](http://www.medicinesforchildren.org.uk) and [www.choiceandmedication.org](http://www.choiceandmedication.org), [Valproate - Welcome](#), as well as manufacturers' information.
- Obtain and document patient consent.
- Where a patient lacks capacity the point above must be covered with the carer/ parent.
- Assess for contraindications and cautions (see [section 4](#)) and interactions (see [section 7](#)).
- Conduct required baseline investigations and initial monitoring (see [section 8](#)).
- Initiate and optimise treatment as outlined in [section 5](#).

- Adhere to the regulatory requirements with regards to the safe initiation and continuation of valproate treatment in light of the possible effects on an unborn child.
- Obtain the agreement of a second specialist that valproate is indicated and is the only suitable treatment for the individual.
- Provide a copy of the Annual Risk Acknowledgement Form (ARAF) to the primary care prescriber, and to the patient or their carer and continue to provide this annually.
- Transfer to primary care is normally after the patient is stabilised on treatment, is seizure free or mental health stable, and has been treated for 3 months and with satisfactory investigation results for at least 4 weeks. Prescribe sufficient medication (note, this may involve a number of prescriptions of shorter durations) to enable transfer to primary care, including where there are unforeseen delays to transfer of care.
- Once treatment is optimised, complete the shared care documentation and send to patient's GP practice detailing the diagnosis, current and ongoing dose, baseline and most recent test results, confirm the monitoring schedule and when the next monitoring is required. Include contact information ([section 13](#)).
- Conduct the required monitoring in [section 8](#) and communicate the results to primary care. After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in [section 9](#) remains appropriate.
- Give advice to primary care on continuing treatment if a woman becomes or wishes to become pregnant or breastfeed. *Ideally under a joint consultant led clinic with the obstetrician.*
- Provide advice to primary care on the management of adverse effects if required.

## Second Specialist responsibilities

- Provide expert, independent clinical opinion on the initiation or continuation of valproate treatment in accordance with the regulatory requirements set out by the [MHRA](#), that there is no other effective or tolerated treatment or there are compelling reasons why the reproductive risks do not apply.
- Countersigning specialist must complete and sign the Annual Risk Acknowledgment Form:
  - for new patients at initiation of valproate treatment.
  - for existing patients, only at their next annual review, unless their circumstances change.

## Primary care responsibilities

- If accepted, prescribe ongoing treatment as detailed in the specialist's request and as per [section 5](#) taking into any account potential drug interactions in [section 7](#).
- Adjust the dose of valproate prescribed as advised by the specialist.

- Conduct the required monitoring as outlined in [section 9](#).
- Ensure that the regulatory requirements in light of the possible effects on an unborn child, and effects on fertility are met. **These include (and may be extended by MHRA regulations) the requirements for highly effective contraception in people of childbearing potential, ensuring that the person has the patient guide and a copy of their signed Annual Risk Acknowledgement Form** provided by their specialist.
- To remind people taking valproate to inform their GP if they think they may be pregnant, emphasising the importance of not stopping valproate, or contraception before they are reviewed by their specialist.
- Where the regulatory requirements are NOT met (which may be related to contraception, documentation or other aspect specified by the MHRA), to acknowledge that prescribing will be outside of the licence.
- Prescribing outside of the licence is transferred to the primary care physician's care at their discretion. The responsibility will remain with the specialist especially if the risk of pregnancy is considered significant.
- Prescribing outside of the licence may reflect:
  1. prescribing for a licensed indication but without the requirements of the pregnancy prevention plan being fulfilled, or
  2. prescribing for an indication outside those stipulated in the manufacturer's licence but where the requirements of the pregnancy prevention plan are fulfilled, or
  3. prescribing for an indication outside of those stipulated in the manufacturer's licence and non-adherence to the pregnancy prevention programme
- A GP should not be expected to prescribe valproate to a person of childbearing potential outside of the pregnancy prevention programme.
- Note that in some situations a cross-sector multidisciplinary meeting may take place to discuss the continued use outside of the licence, and the ways in which prescribing can be continued in a safe manner.
- Assess for possible interactions with valproate when starting new medicines (see [section 7](#)).
- Manage any adverse effects as detailed in [section 10](#) and discuss with specialist team when required.
- Discuss urgently with the specialist if bone marrow suppression is suspected. Consider also admission to hospital if clinically active, eg bleeding, or infection.
- Discuss other adverse effects with the specialist team as clinically appropriate (see [section 10](#)).
- Refer back to the specialist team for advice if the patient becomes or plans to become pregnant.
- Stop treatment as advised by the specialist.

- Use clinical system coding to accurately document pregnancy prevention programme. These codes can be used for all patients on valproate for any condition licensed or unlicensed

Pregnancy prevention programme	1129761000000105
Pregnancy Prevention Programme STARTED	1129771000000103
Pregnancy Prevention Programme DECLINED	1129801000000100
Pregnancy prevention programme NOT NEEDED	1129791000000104
Pregnancy Prevention Programme DISCONTINUED	1129841000000102
Did not attend Pregnancy Prevention Programme	1129831000000106
Pregnancy Prevention Programme DECLINED BY PARENT	1129821000000109
Valproate Annual Risk Acknowledgement Form (ARAF)	1659031000000103
Valproate Annual Risk Acknowledgement Form COMPLETED	1366401000000107
Referral for Valproate Annual Risk Acknowledgement Form	1366381000000107

### **Patient, parent and/or carer responsibilities**

- Take/ support to take valproate as prescribed and do not stop taking it without speaking to their primary care prescriber or specialist.
- Adhere to the regulatory requirements with regards to the safe initiation and continuation of valproate treatment In light of the possible effects on an unborn child.
- Tell anyone who prescribes them/ the person they are caring for/ their child a medicine that they are taking valproate
- Attend/ support to attend/ bring regularly for monitoring and review appointments with primary care and specialist. Be aware that medicines may be stopped if they do not attend appointments.
- Report/ support patient to/ report on patient's behalf adverse effects to their primary care prescriber. Seek immediate medical attention if they develop any symptoms as detailed in [section 11](#).

- Report the use of any over the counter medications to their/ the person they are caring for prescriber and be aware they should discuss the use of valproate with their pharmacist before purchasing any OTC medicines.
- Inform the specialist or primary care prescriber as soon as possible if they/ their child/ person they are caring for become pregnant or wish to become pregnant.

## 1. Background

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This protocol has been produced to support all prescribers who enter into a shared responsibility arrangements to prescribe valproate, so that they can effectively manage the high risk of severe harm from valproate use. 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 unless there are compelling reasons that the reproductive risks do not apply. For the majority of patients, other effective treatment options are available.

For patients in whom valproate treatment was started prior to February 2024, regulatory requirements as set out by the MHRA are to be followed with regards to the need for ongoing annual reviews, and the clinicians who are to be involved in such reviews.

Patients and/or carers must be given sufficient information regarding valproate efficacy and safety in order to allow shared decision making and balance the risks and benefits in deciding on the best treatment. Valproate use in people of child-bearing potential is continually under review from a safety perspective and it may be subject to change. Prescribers must ensure compliance with up-to-date guidance. Additionally, the following link:

<https://www.gov.uk/government/collections/valproate-safety-measures> provides information to support decision making along with relevant clinical information.

This shared care protocol includes all information required to support safe prescribing in strict accordance with current guidance. It applies to prescribing in people of childbearing potential under the age of 55. It is expected that primary, secondary and tertiary care clinicians comply with its content following local agreement. All healthcare organisations are required to report valproate safety incidents and concerns, including those relating to valproate omission or avoidance, to their patient safety specialists through established reporting mechanisms.

The patient (or parent/carer/responsible person) must understand the risks and consent to treatment and agree to regular pregnancy testing as appropriate.

Where patients are eligible for an annual risk review, this consultation should present the risks of withdrawing valproate or switching to alternative treatments, including the use of visual or other explanatory aids to support patients to understand their personalised risk. See [section 11](#) for information on risk communication materials and decision support tools. The risks of any loss of seizure control, a potential increased risk of sudden death in epilepsy (SUDEP), and deterioration of mental health on withdrawal of valproate should also be discussed. When deprescribing valproate, this should be tapered down gradually under the supervision of a specialist.

### **Specific requirements for female patients**

The conditions of the valproate pregnancy prevention programme as set out in the collection of documents available via <https://www.gov.uk/government/collections/valproate-safety-measures> need to be maintained throughout the period of use of valproate medicines until discontinued. This includes patients who are switching to a therapy other than valproate medicines – the conditions of Pregnancy Prevention Programme should be continued until valproate has been discontinued. See [section 12](#) for more detail.

Patients must fulfil all the requirements of the Pregnancy prevention Programme. The only exceptions are when:

- The absence of risk of pregnancy is permanent (e.g., post-menopausal patients or those after hysterectomy).
- The absence of risk may change (e.g., the patient is pre-menarche). Although the pregnancy prevention programme (“Prevent”) does not apply to these patients, their treatment with valproate must be reviewed regularly and at least annually.

In these circumstances the decision to prescribe a valproate medicine must be made following careful discussion, with informed consent from the patient, parent, or carer, and, where appropriate, using a Best Interests process.

The reasons why the patient does not need to be enrolled on Pregnancy Prevention Programme should be documented on the [Annual Risk Acknowledgment Form](#). The patient or carer or parent should countersign the Annual Risk Acknowledgment Form where possible, to confirm the exception is in place and that risks have been discussed. If the absence of risk may change,

the date for the next annual review must be documented and the patient, parent or carer asked to contact the specialist rapidly if the situation changes before that date.

Full details of the Pregnancy Prevention Programme and the accompanying risk management materials are available from <https://www.gov.uk/government/collections/valproate-safety-measures>.

### **Further clinical advice**

This document does not provide clinical advice on patient-specific scenarios. Clinicians should also refer to published guidance such as “Guidance Document on Valproate Use in Women and Girls of Childbearing Years. Shakespeare J., Sisodiya SM. On behalf of the Royal College of General Practitioners and Association of British Neurologists and Royal College of Physicians. Version 2.1, January 23rd 2021.”

### **Changes to the MHRA regulations surrounding the safe prescribing, dispensing and administration of valproate-containing medicines**

It is expected that with ongoing experience of the implementation of the MHRA regulations around valproate as set out in January 2024 there will be further changes to these regulations. Changes to the process for safe prescribing, dispensing and administration of valproate containing medicines as set out by the MHRA will supersede information contained within this shared care document.

### **Definitions**

To retain consistency with publications from the MHRA, the terms Female and Male will be used to denote people with and without childbearing potential.

Male sex: a person with the capacity for sex and reproductive organs including but not limited to having a penis, scrotum, testicles, vas deferens, prostate, producing sperm (small gametes) and/or having chromosomes that are typically (but not always) XY.

Female sex: a person with the capacity for sex and reproductive organs including but not limited to having a vagina, cervix, womb, ovaries, childbearing potential, producing large egg gametes, mammary glands with milk producing potential and/or chromosomes that are typically (but not always) XX.

We recognise and respect that some individuals may identify as transgender which may not adhere to the definitions given above. A transgender person can also change their legal sex by obtaining a Gender Recognition Certificate.

**Ethical considerations:** People are still being born today exposed to sodium valproate in utero despite the fetotoxic and teratogenic risk being well recognised. Valproate has caused physical and neurodevelopmental harm and many of those exposed to valproate in utero have lifelong disabilities. However, it must also be acknowledged that valproate medicines are the most effective treatment for people with certain types of life-threatening epilepsy. To fulfil [legal](#), [GMC](#), and [Montgomery](#) judgement informed choice principles, patients, parents and carers must be given appropriate information regarding valproate efficacy and safety in order to balance the risks and benefits and decide on the best treatment for them. There are a number of innately complex practical and ethical considerations regarding valproate use and requirements of the “Prevent – the valproate pregnancy prevention programme”. In particular:

- People who are able to become pregnant and are unwilling to use long-term highly effective contraception for personal, religious, or health reasons.
- People with learning disabilities must not be presumed to not be sexually active.
- People with life-threatening symptoms that can only be controlled by valproate.
- Assume a person has the capacity to make a decision themselves, unless it's proved otherwise. Wherever possible, help people to make their own decisions.

For people with learning disabilities to be involved in the decision-making process, the requirements of the Mental Capacity Act must be met. People with learning disabilities should NOT be presumed not to be sexually active. All patients should be reviewed by their specialist, who is responsible for assessing their capacity relating to decisions regarding choice of medication. Where appropriate the specialist should enter into discussion with the GP regarding the patient’s capacity and decisions relating to contraception and childbearing. If the patient lacks capacity, then the specialist is responsible for initiating -discussions to decide what is in a person’s best interests, as per the principles of Mental capacity act 2005. For circumstances in which a pregnancy prevention programme (PPP) is NOT appropriate, records must be retained of the decisions taken, their justifications, and who was involved in decision-making. Completion of an initial risk acknowledgment form is still required. Consider a PPP if capacity may change. Clinicians are advised to observe advice from their healthcare regulators for such ethical considerations to ensure they meet statutory duties and professional responsibilities. Valproate medicines should NOT be used in patients of childbearing potential (including young girls who are likely to need treatment into their childbearing years) unless:

- other options are unsuitable, and

- the pregnancy prevention programme (PPP) is in place, or
- certain circumstances exist, such as those outlined below
- The patient, parent or carer must understand the risks and consent to treatment and agree to regular pregnancy testing as appropriate.

All patients should be reviewed by their specialist annually and, where it is deemed appropriate for the individual patient, valproate should be withdrawn if alternative and safer treatments are suitable. Any review should present the risks of withdrawing valproate or switching to alternative treatments, including the use of visual or other explanatory aids to support patients to understand their personalised risk. The risks of any loss of seizure control, a potential increased risk of sudden death in epilepsy (SUDEP), and deterioration of mental health on withdrawal of valproate should also be discussed. When deprescribing valproate, this should be tapered down gradually under the supervision of a specialist.

Valproate medicines should only be used if the conditions of “Prevent – the valproate pregnancy prevention programme” are fulfilled, need to be maintained throughout the period of use of valproate medicines until discontinued. This includes when patients are switching to a therapy other than valproate medicines and should be continued until valproate has been discontinued. The only exceptions are when:

- The absence of risk of pregnancy is permanent (e.g., post-menopausal patients or those after hysterectomy).
- The absence of risk may change (e.g., the patient is pre-menarche). Although the pregnancy prevention programme (“Prevent”) does NOT apply to these patients, their treatment with valproate must be reviewed regularly and at least annually.

Where the patient permanently lacks capacity to consent to sexual activity, in these circumstances the decision to prescribe a valproate medicine must be made following careful discussion, with the parent, carer or Legal power of attorney (health and welfare), and, where appropriate, following a Best Interests process. The reasons why the patient does NOT need to be enrolled on “Prevent – the valproate pregnancy prevention programme” i.e. the potential for NOT becoming pregnant is permanent, it should be documented on the initial Annual Risk Acknowledgment Form. The patient or responsible person should countersign the Annual Risk Acknowledgment Form where possible, to confirm the exception is in place and that risks have been discussed and further annual risk will no longer be required. If the absence of risk may

change, the date for the next annual review must be documented and the patient, parent or carer asked to contact the specialist rapidly if the situation changes before that date.

## 2. Indications

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- Epilepsy
- Treatment of mania in bipolar disorder
- Continuation of treatment after a manic episode
- Mood stabiliser in mood disorders and primary psychotic disorders, under the direction of a consultant psychiatrist ‡
- Prevention of atypical antipsychotic-induced seizures ‡
- Management of compulsive and aggressive behaviour ‡

‡ Off-label indications. Please note licensed indications vary by form and manufacturer. Please see SPCs for details. **Inclusion in the list above does NOT indicate that valproate is appropriate to be prescribed in these off-label indications and NICE or other guidance on appropriateness should be reviewed prior to initiation.** When prescribing valproate off-label, the specialist should be satisfied that an alternative, licensed medicine would NOT meet the patient's needs, in line with GMC ethical guidance on prescribing unlicensed medicines. All patients where the Pregnancy Prevention Programme applies should be reviewed by their specialist at least annually, and valproate should be withdrawn where there are alternative and safer treatments available. When deprescribing valproate, this should be tapered down gradually under the supervision of a specialist.

## 3. Locally agreed off-label use [Back to top](#)

The Frimley Health Integrated Care System Medicines Board recommended the use of this document for the indications as outlined above.

The following information should be provided in correspondence to support prescribing in line with this shared care.

- Dosing specific to the indication
- Relevant interaction information
- Any additional monitoring requirements
- Duration of treatment

- Frequency of review.
- Specific features of adverse effects or deterioration pertinent to the specific indication for which it is used.

## 4. Contraindications and cautions

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This information does not replace the Summary of Product Characteristics (SPC), and should be read in conjunction with it. Please see [BNF](#) & [SPC](#) for comprehensive information.

### Contraindications:

- Hypersensitivity to valproate medicines or any other ingredient in the desired preparation
- Pregnancy (unless prescribed for epilepsy and no suitable alternative exists)
- In people of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled.
- Active liver disease
- Personal or family history of severe hepatic dysfunction, particularly drug-related
- Known or suspected mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase (POLG)
- Acute porphyrias
- Urea cycle disorders

### Cautions:

- Hepatic impairment
- Systemic lupus erythematosus
- Renal impairment: dose reduction may be required
- Diabetes (ketone bodies may give false positive urinalysis results)
- Carnitine palmitoyltransferase (CPT) type II deficiency
- Alcohol consumption: manufacturers do not recommend during treatment with valproate. Patients should be advised to moderate their alcohol consumption to no more than 14 units per week.
- Suicidal ideation (evidence of association being due to medication is inconclusive).
- Weight or BMI outside healthy range (BMI > 35 kg/m<sup>2</sup>).
- Long term use of valproate is associated with decreased bone mineral density. For more information see Drug Safety Update April 2009, vol 2 issue 9: 2.

## 5. Initiation and ongoing dose regimen

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- Transfer of monitoring and prescribing to primary care is normally after at least 12 weeks, and when the patient's dose has been optimised and with satisfactory investigation results for at least 4 weeks and the patient's condition stable.
- The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.
- All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.
- Termination of treatment will be the responsibility of the specialist.

Valproate medicines may only be initiated in people of childbearing potential aged under 55 if the conditions of the Pregnancy Prevention Programme are fulfilled, unless exceptions apply (see [section 1](#)).

Specific dosing advice relating to the different valproate preparations (formulation and release profile) is provided by the manufacturer for the different licensed indications. Published dosing information should be referred to for both initiation and ongoing maintenance treatment

## 6. Pharmaceutical aspects

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Route of administration:	<b>Oral</b>
Formulation:	<ul style="list-style-type: none"><li>• Modified release and immediate release preparations are available. Products may be available as tablets, capsules, granules, chewable tablets and liquid preparations.</li></ul>
Administration details:	<p>Valproate medicines should preferably be prescribed as monotherapy and at the lowest effective dose.</p> <p>Doses should be taken regularly, at the same time every day.</p> <p>If a dose is missed, it should be taken as soon as remembered unless it is nearly time for the next dose. <b><u>A double dose should not be taken to make up for a missed dose.</u></b></p>
Other important information:	<p><b>Continuity of supply of a specific product</b></p> <p>The MHRA classify valproate medicines as a category 2 antiepileptic drug. When used for epilepsy, the need for continued supply of a particular</p>

manufacturer's product should be based on clinical judgement and consultation with the patient and/or carer, considering factors such as seizure frequency and treatment history. See [MHRA advice](#) for more information. In case of availability problems, discuss with the specialist team for advice on the best course of action for the individual patient.

### **False positive laboratory tests**

Valproate medicines may cause false positive urine tests for ketones.

## **7. Significant medicine interactions**

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The following list is not exhaustive. Please see [BNF](#) or [SPC](#) for comprehensive information and recommended management.

- Anti-seizure medicines: concomitant use of multiple anti-seizure medicines may increase the risk of teratogenicity. Individual risk assessment is required.
- Antipsychotics, monoamine oxidase inhibitors, antidepressants, and benzodiazepines – valproate may potentiate the effect of other psychotropic medicines. Clinical monitoring is advised and dose adjustment of other drugs may be required.
- Hepatotoxic medicines – may increase the risk of hepatotoxicity.
- Oestrogen-containing medicines, including contraceptives – may increase clearance of valproate and reduce efficacy; monitor clinical response when stopping or starting oestrogen-containing products.
- Acetazolamide – may increase the risk of valproate toxicity.
- Bupropion – exposure increased by valproate; caution advised.
- Cannabidiol – increased risk of ALT elevations
- Carbapenem antibiotics, e.g., ertapenem, imipenem, meropenem – substantial reductions in valproate levels, avoid where possible.
- Guanfacine – increases exposure to valproate, monitor and adjust dose.
- Lamotrigine – lamotrigine exposure increased. Adjust lamotrigine dose and monitor for adverse reactions such as rash.
- Nimodipine – exposure to nimodipine may be increased. Adjust dose.
- Nortriptyline – exposure increased by valproate; monitor.
- Phenytoin and fosphenytoin – levels of phenytoin/fosphenytoin may be increased, and valproate levels may be reduced. Clinical monitoring recommended.
- Pivmecillinam – increased risk of adverse effects.

- Phenobarbital – levels of both drugs may be altered. Monitor and adjust dose if concerns around compliance or toxicity.
- Primidone – primidone levels may be increased. Clinical monitoring advised if concerns around compliance or toxicity. .
- Propofol – propofol concentrations may be increased, dose reduction may be considered.
- Quetiapine – increased risk of neutropenia/leucopenia
- Ritonavir – may reduce valproate concentrations.
- Topiramate – increased risk of toxicity when co-administered with valproate, monitor for signs and symptoms of encephalopathy or hyperammonaemia; may also reduce valproate plasma levels..
- Highly protein bound drugs, e.g. aspirin – may displace valproate, risking toxicity
- Less strongly protein bound drugs, e.g. warfarin – may be displaced by valproate, with possibility of increased therapeutic effects or toxicity.
- Cytochrome P450 inhibitors e.g. erythromycin, fluoxetine, cimetidine – may increase valproate levels.

## 8. Baseline investigations, initial monitoring and ongoing monitoring to be undertaken by specialist

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Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in immediate future will prescribing and monitoring be transferred to primary care.

### **Baseline investigations (all indications):**

If it is not possible to perform baseline investigations prior to initiation (e.g. in an emergency situation), they should be completed as soon as possible after initiation.

- Complete the Annual Risk Acknowledgement Form (people of childbearing potential under the age of 55)
- Serum pregnancy test in people of child-bearing potential. Where this is not considered appropriate for a particular individual, the reasons for not doing so must be documented in the person's patient record, and communicated to the primary care prescriber.
- Urea and electrolytes & GFR
- Full blood count
- Liver function tests, including coagulation screen
- Height, weight, and BMI

### Initial monitoring:

- Monitoring at baseline and during initiation is the responsibility of the specialist, only once the patient is optimised on the chosen medication with no anticipated further changes expected in immediate future will prescribing and monitoring be transferred to the GP.

### Ongoing monitoring and advice:

All patients of child-bearing potential should be reviewed by their specialist annually and valproate should be withdrawn where there are alternative and safer treatments available.

Deprescribing should be undertaken under the supervision of a specialist.

Annual review for people of childbearing potential should include:

- completion of the [Annual Risk Acknowledgement Form](#) and sharing of the form with the GP practice
- discussion regarding contraception, including a prompt to check when long-acting reversible contraceptives (e.g. implants, intrauterine devices) must be renewed

When a patient is reviewed, advise primary care whether treatment should be continued, confirm the ongoing indication for valproate and dose, and whether the ongoing monitoring outlined in [section 9](#) remains appropriate.

## 9. Ongoing monitoring requirements to be undertaken by primary care

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See [section 10](#) for further guidance on management of adverse effects/responding to monitoring results.

Monitoring and advice	Frequency
<ul style="list-style-type: none"><li>Full blood count</li><li>Liver function tests, including prothrombin time</li><li>Weight and BMI</li></ul>	Six months after initiation (as per manufacturer's SPC). “ “ “ “ “ “

Where clinically indicated further monitoring may be required, e.g. prior to surgery, deteriorating renal function, or a change in comorbid conditions.

<p><b>Annual Risk Acknowledgement Form (people of childbearing potential under the age of 55)</b></p> <p>Ensure that patients of childbearing potential have had an annual review with their specialist, and:</p> <ul style="list-style-type: none"> <li>• an up-to-date annual risk acknowledgment form is on file, or</li> </ul> <p>there is a documented permanent absence of risk of pregnancy, e.g. the patient is post-menopause or has had a hysterectomy (see <a href="#">section 1</a>) or permanently lacks capacity and to consent to sexual activity</p>	<p>Annually</p> <p>Where there is a documented permanent absence of risk of pregnancy , this shared care will no longer apply</p>
<p><b>Contraception</b></p> <p>Ensure that patients of childbearing potential have access to an appropriate method of contraception, know how to use it, and are aware of the importance of using it correctly. Where appropriate, offer signposting to providers, e.g. community contraceptive clinic, or sexual health clinics and prompts to check when long-acting reversible contraceptives (e.g. implants, intrauterine devices) must be renewed.</p>	<p>At all patient contacts regarding valproate.</p>
<p><b>Pregnancy testing</b></p> <p>Discuss pregnancy testing and prompt patients to take a test when appropriate. Where possible, offer signposting to providers of free testing, e.g. community contraceptive clinic, or sexual health clinics.</p> <p>Pregnancy testing is recommended:</p> <ul style="list-style-type: none"> <li>• 3 weeks after starting a new contraceptive method, if there was any risk of pregnancy at the start of the contraceptive method.</li> <li>• Whenever there is reason to suggest lack of adherence or effectiveness of contraception</li> </ul> <p>More frequently in patients using a user-dependent method of contraception, e.g. condom, cap, diaphragm, oral contraceptive pills, or fertility awareness-based methods</p>	<p>At all patient contacts regarding valproate.</p>

(If relevant) If monitoring results are forwarded to the specialist team, please include clear clinical information on the reason for sending, to inform action to be taken by secondary care.

## 10. Adverse effects and other management

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**Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)**

For information on incidence of ADRs see relevant summaries of product characteristics

Result	Action for primary care
<p><b>As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance.</b></p>	
<p><b>Pregnancy confirmed</b></p>	<p>Prescribe folic acid 5mg daily immediately if not already taking, and refer to specialist and maternity/obstetrics service urgently (within days). Remind the patient not to stop taking valproate medicine in the interim.</p>
<p><b>Patient planning a pregnancy</b></p>	<p>Refer to specialist; Prescribe folic acid 5mg daily immediately if not already taking. Remind the patient not to stop using contraception or taking valproate medicine in the interim.</p>
<p><b>Full blood count:</b> Red cell count, haemoglobin or platelets below reference range</p>	<p>Contact specialist team for advice; consider monitoring more frequently. Do not stop valproate medicine.</p>
<p>Spontaneous bruising or bleeding, or other signs or symptoms of blood dyscrasias, e.g. purpura, sore throat, fever, or malaise</p>	<p>Continue valproate medicine and discuss with specialist team urgently (same day). Full blood count, liver function tests, and coagulation screen are indicated; discuss most appropriate route with specialist team.</p>
<p>Signs and symptoms of liver dysfunction, e.g.:</p> <ul style="list-style-type: none"> <li>- prolonged prothrombin time (particularly in association with significant decrease in fibrinogen and coagulation factors, decreased albumin, increased bilirubin and raised transaminases)</li> <li>- symptoms including asthenia, malaise, anorexia, lethargy, oedema, drowsiness, repeated</li> </ul>	<p>Repeat LFTs and coagulation screen and discuss urgently with specialist team. Stopping valproate medicine may be indicated while waiting for results, particularly if there is strong suspicion that worsening seizures are due to hepatic dysfunction.</p>

vomiting and abdominal pain, jaundice recurrence of seizures	
<b>Gastrointestinal disorders:</b> Symptoms of pancreatitis, e.g. acute abdominal pain, nausea, or vomiting	Refer for urgent hospital admission if the person has suspected acute pancreatitis, for further management. Do not delay admission by taking blood samples or ordering imaging in primary care.
<b>Psychiatric disorders</b> Suicidal ideation or behaviour	Refer for urgent psychiatric assessment via local pathways e.g. crisis or specialist teams, if appropriate. Notify specialist team. Do not stop valproate medicine.
<b>Weight or BMI outside healthy range</b>	Do not stop valproate medicine. Provide appropriate support on multicomponent interventions to increase physical activity levels, improve eating behaviour and quality of diet. Consider referral to dietician or other local services if relevant comorbidities are present (e.g. heart disease, diabetes) or BMI >35.

## 11. Advice to patients and carers

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The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.

The specialist will counsel the patient with regards to the benefits and risks of treatment and will provide the patient with any relevant information and advice, in a format that the patient can understand, including patient information leaflets on individual medicines.

The specialist should use visual or other explanatory aids to support the patient's understanding of their personalised risk of pregnancy, use of valproate, withdrawing valproate or switching to alternative treatments.

**The patient must be advised to report any of the following signs or symptoms to their primary care prescriber without delay:**

- If they suspect there has been a problem with their contraception or they may be pregnant
- If they are planning a pregnancy
- Symptoms of blood disorders, e.g. unexplained bleeding, bruising, purpura, sore throat, fever, or malaise

- Symptoms of liver disorders, e.g. sudden weakness, malaise, anorexia, lethargy, oedema, drowsiness (especially if accompanied by repeating vomiting and abdominal pain), or jaundice.
- Symptoms of pancreatitis, e.g. abdominal pain, nausea, or vomiting
- Suicidal ideation or behaviour.

The patient should be advised to:

- Report any side effects to their primary care prescriber, e.g. weight gain. Not stop taking valproate medicines without first discussing this with their doctor, especially if taking for epilepsy (risk of status epilepticus and sudden unexpected death in epilepsy (SUDEP)).
- Ensure other healthcare providers are aware of valproate medicine use (for example, coagulation blood tests may be needed prior to surgery).
- In patients of childbearing potential, they must use an appropriate form of contraception, as agreed with their doctor/nurse/sexual health service.
- Take a pregnancy test whenever they suspect there is a chance they could be pregnant.

This includes:

- Three weeks after starting a new method of contraception, particularly if there was any risk of pregnancy at the start of the new method
- Whenever there is any reason to doubt that contraception has been effective, e.g. missed pill, broken condom, missed or late menstrual period
- Whenever a health professional recommends or offers a pregnancy test
- See NHS advice on when to do a pregnancy test, and where to get one: <https://www.nhs.uk/pregnancy/trying-for-a-baby/doing-a-pregnancy-test/>
- Not drive or operate machines if valproate affects their ability to do so safely. Patients with a diagnosis which affects their ability to drive must notify the Driver and Vehicle Licensing Agency (DVLA); see <https://www.gov.uk/driving-medical-conditions>.
- Tell anyone who prescribes them a medicine that they are taking a valproate medicine. Always tell a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe.

Valproate can affect bone density. People taking valproate should consider taking vitamin D supplements; see <https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/>

**Patient information:**

NHS.uk, sodium valproate <https://www.nhs.uk/medicines/sodium-valproate/>

NHS.uk Contraception Guide: <https://www.nhs.uk/conditions/contraception/>

Pregnancy prevention programme patient guide and patient card:

<https://www.gov.uk/government/collections/valproate-safety-measures>

MHRA: epilepsy medicines and pregnancy

[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/950069/Epilepsy-medicines-in-pregnancy-leaflet.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950069/Epilepsy-medicines-in-pregnancy-leaflet.pdf)

Choice and Medication website **SABP**- <https://www.choiceandmedication.org/sabp/printable-leaflets/patient-information-leaflets/139/ALL/> or

Choice and Medication website **BHFT**» [Printable leaflets \(choiceandmedication.org\)](https://www.choiceandmedication.org)

NHS England Easy Read valproate PIL [Valproate - Welcome](#)

## 12. Pregnancy, paternal exposure and breast feeding

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It is the responsibility of the specialist to provide advice on the need for contraception on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist.

**Pregnancy:**

Valproate is highly teratogenic and evidence supports that use in pregnancy leads to physical birth defects in 10 in every 100 babies (compared with a background rate of 2 to 3 in 100) and neurodevelopmental disorders in approximately 30 to 40 in every 100 children born to mothers taking valproate.

In patients of childbearing potential valproate medicines must be initiated and supervised by an appropriate specialist experienced in the management of the patient's condition. Valproate medicines should not be used in patients of childbearing potential unless other treatments are ineffective or not tolerated, or in circumstances as outlined in [section 1](#).

If valproate is prescribed, at least one highly effective method of contraception (preferably a user independent form such as an intrauterine device or implant) or two complementary forms of contraception including a barrier method should be used.

For children or patients without the capacity to make an informed decision, provide the information and advice on highly effective methods of contraception and on the use of valproate medicines during pregnancy to their parent or carer and make sure they clearly understand the content.

Further information for healthcare professionals:

<https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-SODIUM-VALPROATE-IN-PREGNANCY/>

Further information on contraception is available from the Royal College of Psychiatrists:

<https://www.rcgp.org.uk/-/media/Files/CIRC/Epilepsy/Guidance-on-Valproate-use---Dec-2020.ashx?la=en>

Further information for patients:

<https://www.medicinesinpregnancy.org/Medicine--pregnancy/Sodium-valproate/>

### **Breastfeeding:**

Valproate medicines are suitable for use in breastfeeding but the conditions of “Prevent – the valproate pregnancy prevention programme” must be met, including that other treatments are ineffective or not tolerated, or in circumstances as outlined in [section 1](#)

Valproate is excreted in breast milk in small amounts. Infants should be monitored for adverse effects such as jaundice, bruising, and bleeding.

For more information see the following SPS resources:

- Sodium valproate: <https://www.sps.nhs.uk/medicines/sodium-valproate/>
- Valproic acid: <https://www.sps.nhs.uk/medicines/valproic-acid/>
- Safety in lactation: control of epilepsy: <https://www.sps.nhs.uk/articles/safety-in-lactation-control-of-epilepsy/>
- Safety in Lactation: Drugs for bipolar disorder and hypomania: <https://www.sps.nhs.uk/articles/safety-in-lactation-drugs-for-bipolar-disorder-hypomania/>

### **The valproate pregnancy prevention programme:**

Valproate medicines may be initiated only if the conditions of the Pregnancy Prevention Programme are fulfilled, or in circumstances as outlined in [section 1](#). The conditions of the Pregnancy Prevention Programme need to be maintained throughout the period of use of valproate medicines. This includes patients who are switching to a therapy other than valproate

medicines – the conditions of the Pregnancy Prevention Programme should be continued until valproate has been discontinued.

### **Roles and responsibilities of healthcare professionals**

The Guide for healthcare professionals (HCPs), part of Pregnancy Prevention Programme outlines actions for HCPs involved in the treatment of epilepsy or bipolar disorder, including specialists, general practitioners, gynaecologists/obstetricians, midwives, nurses, pharmacists and emergency physicians. For full details visit

<https://www.gov.uk/government/collections/valproate-safety-measures>

Available resources include:

- booklet for healthcare professionals
- booklet for patients
- patient card
- annual risk acknowledgement form

## **13. Specialist contact information**

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Name: *[insert name]*

Role and specialty: *[insert role and specialty]*

Daytime telephone number: *[insert daytime telephone number]*

Email address: *[insert email address]*

Alternative contact: *[insert contact information, e.g. for clinic or specialist nurse]*

Out of hours contact details: *[insert contact information, e.g. for duty doctor]*

## **14. Additional information**

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Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed. Ensure that the specialist is informed in writing of any changes to the patient's GP or their contact details.

## **15. References**

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- <https://www.gov.uk/government/collections/valproate-safety-measures>

- [www.medicines.org.uk](http://www.medicines.org.uk)

## 16. Other relevant national guidance

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- NHSE/NHSCC guidance – items which should not be routinely prescribed in primary care: guidance for CCGs  
NHSE policy- Responsibility for prescribing between Primary & Secondary/Tertiary Care  
Bipolar disorder: assessment and management. NICE CG 185.  
<https://www.nice.org.uk/guidance/cg185>
- Epilepsies in children, young people and adults. NICE NG217.  
<https://www.nice.org.uk/guidance/ng217>

## 17. Local arrangements for referral

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Define the referral procedure from hospital to primary care prescriber & route of return should the patient's condition change.

**To be agreed and completed locally**

**Medicines board date: November 2024**

**Last updated: October 2024**

## Appendix 1: Shared Care Request letter (Specialist to Primary Care Prescriber)

Dear *[insert Primary Care Prescriber's name]*

Patient name: *[insert patient's name]*

Date of birth: *[insert date of birth]*

NHS Number: *[insert NHS Number]*

Diagnosis: *[insert diagnosis]*

As per the agreed *[insert APC name]* shared care protocol for *[insert medicine name]* for the treatment of *[insert indication]*, this patient is now suitable for prescribing to move to primary care.

The patient fulfils criteria for shared care and I am therefore requesting your agreement to participate in shared care. Where baseline investigations are set out in the shared care protocol, I have carried these out.

I can confirm that the following has happened with regard to this treatment:

	Specialist to complete
<i>The patient has been initiated on this therapy and has been on an optimised dose for the following period of time:</i>	
<i>Baseline investigation and monitoring as set out in the shared care documents have been completed and were satisfactory</i>	Yes / No
<i>The condition being treated has a predictable course of progression and the patient can be suitably maintained by primary care</i>	Yes / No
<i>The risks and benefits of treatment have been explained to the patient</i>	Yes / No
<i>The roles of the specialist/specialist team/ Primary Care Prescriber / Patient and pharmacist have been explained and agreed</i>	Yes / No
<i>The patient has agreed to this shared care arrangement, understands the need for ongoing monitoring, and has agreed to attend all necessary appointments</i>	Yes / No
<i>I have enclosed a copy of the shared care protocol which covers this treatment/the SCP can be found here (insert electronic/ web link)</i>	Yes / No
<i>I have included with the letter copies of the information the patient has received</i>	Yes / No
<i>I have provided the patient with sufficient medication to last until</i>	
<i>I have arranged a follow up with this patient in the following timescale</i>	

Treatment was started on *[insert date started]* and the current dose is *[insert dose and frequency]*.

If you are in agreement, please undertake monitoring and treatment from *[insert date]*

NB: date must be at least 1 month from initiation of treatment.

The next blood monitoring is due on *[insert date]* and should be continued in line with the shared care guideline.

Please respond to this request for shared care, in writing, within 14 days of the request being made where possible.

## Appendix 2: Shared Care Agreement Letter (Primary Care Prescriber to Specialist)

### Primary Care Prescriber Response

Dear *[insert Doctor's name]*

Patient *[insert Patient's name]*

NHS Number *[insert NHS Number]*

Identifier *[insert patient's date of birth and/or address]*

Thank you for your request for me to accept prescribing responsibility for this patient under a shared care agreement and to provide the following treatment

Medicine	Route	Dose & frequency

I can confirm that I am willing to take on this responsibility from *[insert date]* and will complete the monitoring as set out in the shared care protocol for this medicine/condition.

Primary Care Prescriber signature: \_\_\_\_\_ Date:  
\_\_\_\_\_

Primary Care Prescriber address/practice stamp

## Appendix 3: Shared Care Refusal Letter (Primary Care Prescriber to Specialist)

**Re:**

Patient *[insert Patient's name]*

NHS Number *[insert NHS Number]*

Identifier *[insert patient's date of birth and/or address]*

Thank you for your request for me to accept prescribing responsibility for this patient.

In the interest of patient safety NHS *[insert CCG name]*, in conjunction with local acute trusts have classified *[insert medicine name]* as a Shared Care drug, and requires a number of conditions to be met before transfer can be made to primary care.

**I regret to inform you that in this instance I am unable to take on responsibility due to the following:**

		Tick which apply
1.	<p><b>The prescriber does not feel clinically confident in managing this individual patient's condition, and there is a sound clinical basis for refusing to accept shared care</b></p> <p>As the patients primary care prescriber I do not feel clinically confident to manage this patient's condition because <i>[insert reason]</i>. I have consulted with other primary care prescribers in my practice who support my decision. This is not an issue which would be resolved through adequate and appropriate training of prescribers within my practice.</p> <p><b>I have discussed my decision with the patient and request that prescribing for this individual remain with you as the specialist, due to the sound clinical basis given above.</b></p>	
2.	<p><b>The medicine or condition does not fall within the criteria defining suitability for inclusion in a shared care arrangement</b></p> <p>As the medicine requested to be prescribed is not included on the national list of shared care drugs as identified by RMOC or is not a locally agreed shared care medicine I am unable to accept clinical responsibility for prescribing this medication at this time.</p> <p><b>Until this medicine is identified either nationally or locally as requiring shared care the responsibility for providing this patient with their medication remains with you</b></p>	
3.	<p><b>A minimum duration of supply by the initiating clinician</b></p> <p>As the patient has not had the minimum supply of medication to be provided by the initiating specialist I am unable to take clinical</p>	

	<p>responsibility for prescribing this medication at this time. Therefore can you please contact the patient as soon as possible in order to provide them with the medication that you have recommended.</p> <p><b><i>Until the patient has had the appropriate length of supply the responsibility for providing the patient with their medication remains with you.</i></b></p>	
4.	<p><b>Initiation and optimisation by the initiating specialist</b></p> <p>As the patient has not been optimised on this medication I am unable to take clinical responsibility for prescribing this medication at this time. Therefore can you please contact the patient as soon as possible in order to provide them with the medication that you have recommended.</p> <p><b><i>Until the patient is optimised on this medication the responsibility for providing the patient with their medication remains with you.</i></b></p>	
5.	<p><b>Shared Care Protocol not received</b></p> <p>As legal responsibility for clinical care lies with the clinician who signs the prescription, I need to ensure that I am in possession of sufficient clinical information for me to be confident to prescribe this treatment for my patient and it is clear where each of our responsibilities lie to ensure the patient is safely managed.</p> <p>For this reason I am unable to take clinical responsibility for prescribing this medication at this time, therefore would you please contact the patient as soon as possible in order to provide them with the medication that you have recommended.</p> <p><b><i>Until I receive the appropriate SCP, responsibility for providing the patient with their medication remains with you.</i></b></p>	
6.	<p><b>Other (Primary Care Prescriber to complete if there are other reasons why shared care cannot be accepted)</b></p>	

I would be willing to consider prescribing for this patient once the above criteria have been met for this treatment.

NHS England 'Responsibility for prescribing between Primary & Secondary/Tertiary care' guidance (2018) states that "when decisions are made to transfer clinical and prescribing responsibility for a patient between care settings, it is of the utmost importance that the GP feels clinically competent to prescribe the necessary medicines. It is therefore essential that a transfer involving medicines with which GPs would not normally be familiar should not take place without full local agreement, and the dissemination of sufficient, up-to-date information to individual GPs." In this case we would also see the term GP being interchangeable with the term Primary Care Prescriber.

Please do not hesitate to contact me if you wish to discuss any aspect of my letter in more detail and I hope to receive more information regarding this shared care agreement as soon as possible

Yours sincerely

**Primary Care Prescriber signature:** \_\_\_\_\_  
**Date:** \_\_\_\_\_

**Primary Care Prescriber address/practice stamp**