NHS Somerset

# *Shared Care Protocol*
# *Valproate medicines for all patients (male or female) for all indications*

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*This shared care protocol (SCP) sets out details for the sharing of care for* ***all patients prescribed valproate (as sodium valproate, valproate semisodium, or valproic acid) in the management of any indication (including off-label use).***

*It should be read in conjunction with the latest Summary of Products Characteristics (SmPC) available at http://www.medicines.org.uk/emc/*

*As outlined in NHS England Guidance 2018 (07573), 'Responsibility for Prescribing Between Primary & Secondary/Tertiary Care': When a specialist considers a patient's condition to be stable or predictable, they may seek the agreement of the GP concerned (and the patient) to share their care.*

*This document provides information on drug treatment for the shared commitment between the specialist and GP concerned. GPs are invited to participate. If the GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.*

*N.B. If the GP decides not to participate in shared care for a particular patient, they must inform the relevant specialist in writing, within 2 weeks of receipt of a request to share care.*

## Introduction:

Valproate (as sodium valproate, valproate semisodium, or valproic acid; brand names Epilim®, Depakote®, Convulex®, Episenta®, Epival®, Syonell®, Belvo® and Dyzantil®) is approved in the UK to treat epilepsy and bipolar disorder. It is also sometimes used outside of the licence ('off label') to treat other conditions. Valproate can cause serious harm to an unborn baby if it is taken during pregnancy. Due to these risks, it has been advised for some time that valproate should only be used in girls or in any woman able to have children (people of childbearing potential) if other treatments do not work (ineffective) or are not tolerated. If valproate is used in females of childbearing potential then the conditions of the Pregnancy Prevention Programme need to be followed. The Pregnancy Prevention Programme is designed to make sure patients are fully aware of the risks of valproate and agree to take steps to avoid becoming pregnant while taking this medicine.

The MHRA issued a patient safety alert on the risks associated with valproate for the under 55s in November 2023.

New regulatory measures in January 2024 for oral valproate mean that:

1. **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. For the majority of patients, other effective treatment options are available.**

2. **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.**

In September 2024, the MHRA issued precautionary advice for **men** taking valproate and their partners to use effective contraception because of new data suggesting a potential small increased risk of harm to children if valproate is used by a father around the time of conception.

In February 2025, the CHM advised that a review by two specialists is required for initiating valproate in patients under 55 years of age but not for men who are already taking valproate. Three infographics have been produced to clarify in which situations review by two specialists may be required:

- for female patients under 55 years old
- for male patients under 55 years old
- for male and female patients 55 years and older

**MHRA/CHM advice:**

Valproate use by women and girls - GOV.UK (www.gov.uk) Updated 28 Nov 2023

Valproate safety measures - GOV.UK (www.gov.uk) Updated 22 Jan 2024

Valproate: review of safety data and expert advice on management of risks - GOV.UK (www.gov.uk) Published 28 Nov 2023

Full pack dispensing of valproate-containing medicines - GOV.UK (www.gov.uk) Published Oct 2023

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 Nov 2023

MHRA update on new study on risk in children born to men taking valproate - GOV.UK (www.gov.uk)

CAS-ViewAlert (mhra.gov.uk) Valproate: important new regulatory measures for oversight of prescribing to new patients and existing female patients. Published 22 February 2024

Valproate use in men: as a precaution, men and their partners should use effective contraception - GOV.UK (www.gov.uk) Published 5 September 2024

Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): review by two specialists is required for initiating valproate but not for male patients already taking valproate - GOV.UK Published 13 Feb 2025

## 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 and/or 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 who lack capacity.
- 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

For people who lack capacity to be involved in the decision-making process, the requirements of the Mental Capacity Act must be met. 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 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 a Best Interest Meeting/ Process.

For circumstances in which a pregnancy prevention programme (PPP) is not appropriate, records must be kept of which decisions are taken, their justifications, and who was involved in decision-making. Completion of an Annual Risk Acknowledgment Form is still required. 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 (or parent/caregiver/responsible person) 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, except as detailed below.
The conditions of "Prevent – the valproate pregnancy prevention programme" 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 "Prevent – the valproate pregnancy prevention programme" should be continued until valproate has been discontinued.

If the patient does not need to be enrolled on "Prevent – the valproate pregnancy prevention programme," the reasons should be documented on the 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.

If the absence of risk may change, the date for the next annual review should be documented and the patient, parent or carer asked to contact the specialist rapidly if the situation changes before that date.

Full details of "**Prevent – the valproate pregnancy prevention programme**" and the accompanying risk management materials are available from the MHRA website.

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

Available resources include:

- Patient guide
- Healthcare Professional Guide
- Annual Risk Acknowledgement Form
- Risk Acknowledgement Form for male patients starting valproate
- Patient card

## Licensed Indications:

- Epilepsy
- Bipolar disorder

Licensed indications vary by product and manufacturer. See SmPC for details.

**Off-label use: restrictions and responsibilities still apply**
Valproate is not licensed for treatment of conditions other than epilepsy or bipolar disorder in the UK. However, these medicines are sometimes used off-label (for example, in migraine prophylaxis). All females of childbearing potential should meet the conditions of a Pregnancy Prevention Programme, irrespective of indication. All prescribers should be aware of their responsibilities when prescribing off-label.

Off-label or unlicensed use of medicines: prescribers' responsibilities - GOV.UK (www.gov.uk)

## Dose (posology & method of administration):

Consult product literature for full details as dosage information varies between products http://www.medicines.org.uk/emc/

- **Sodium valproate or valproic acid:**

Adults and children 12 years and over:
Initially 600 mg daily, increasing in 150-300 mg increments at intervals of at least 3 days until control is achieved. Slower titration may be appropriate, particularly in neurology.
Maintenance dose usually 1000 – 2000 mg daily, i.e., 20-30 mg/kg. Where adequate control is not achieved within this range the dose may be up to 2500 mg per day.

Children over 20 kg:
Initially up to 400 mg daily, increased at intervals until control is achieved.
Maintenance dose usually in the range 20-30 mg/kg daily. Maximum dose 35 mg/kg daily.

- **Valproate semisodium:**

Adults:
Up to 750 mg daily in 2-3 divided doses. Increased incrementally to the lowest dose which produces the desired effect.
Maintenance dose usually 1000 – 2000 mg daily. Patients receiving daily doses exceeding 45 mg/kg daily should be carefully monitored.

Efficacy in children below 18 years has not been established.

## Contra-indications:

For full details see individual SmPCs at http://www.medicines.org.uk/emc/

- **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**
- Pregnancy (unless prescribed for **epilepsy** and **two specialists independently consider and document that there is no other effective or tolerated treatment)**
- Patients of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled
- Male patients of any age should not donate sperm during valproate treatment and for 3 months after stopping valproate
- Hypersensitivity to the active substance or to any of the excipients
- 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

## Special warnings and precautions:

For full details see individual SmPCs at http://www.medicines.org.uk/emc/

- Male patients (of any age) who may father children (see 'Paternal exposure and risk to children' below)
- Risk of hepatic impairment – monitor liver function
- Systemic lupus erythematosus (SLE) - potential benefit of valproate should be weighed against its potential risk in patients with SLE
- Renal impairment - dose reduction may be required
- Suicidal ideation and behaviour – Patients/carers should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge - see MHRA alert Antiepileptics: risk of suicidal thoughts and behaviour - GOV.UK (www.gov.uk)
- The concomitant use of valproic acid/sodium valproate and carbapenem agents is not recommended
- Pancreatitis: Patients should be advised to consult their doctor immediately if they develop symptoms suggestive of pancreatitis (e.g. abdominal pain, nausea and vomiting, monitor serum amylase)
- Weight gain: Valproate very commonly causes weight gain, which may be marked and progressive. All patients should be warned of this risk at the initiation of therapy and appropriate strategies adopted to minimise weight gain
- Patients with known or suspected mitochondrial disease: POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders
- Alcohol intake is not recommended during treatment with valproate.

- Long term use of valproate is associated with decreased bone mineral density – see MHRA alert Antiepileptics: adverse effects on bone - GOV.UK (www.gov.uk)
- Diabetes - ketone bodies may give false positive urinalysis results
- Carnitine palmitoyltransferase (CPT) type II deficiency - greater risk of rhabdomyolysis

**Continuity of supply of a specific product**
The MHRA classify valproate medicines as a category 2 antiepileptic drug. When used for epilepsy, the need for continued supply of a particular 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.

## Drug interactions:

For full details see BNF and individual SmPCs at http://www.medicines.org.uk/emc/

- **Anti-seizure medicines:** concomitant use of multiple anti-seizure medicines may increase the risk of teratogenicity. Individual risk assessment is recommended.
- **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 hepatoxicity
- **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
- **Carbapanem 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.
- **Nortiptylline** – exposure increased by valproate; monitor.
- **Phenytoin and fosphenytoin** – levels of phenytoin/fosphenytoin and valproate medicines may both be altered. Clinical monitoring recommended.
- **Pivmecillinam** – increased risk of adverse effects.
- **Phenobarbital** – levels of both drugs may be altered. Monitor and adjust dose.
- **Primidone** – primidone levels may be increased. Clinical monitoring advised.
- **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
- **Highly protein bound drugs, e.g.** aspirin – may displace valproate, risking toxicity

## Fertility, pregnancy and lactation:

**Pregnancy:**
Valproate has a high teratogenic potential. Exposure of an unborn child to valproate in utero is associated with a high risk of congenital malformations (11%) and neurodevelopmental disorders (30–40%), which may lead to permanent disability. The available evidence does not support a specific at-risk gestational period and the possibility of a risk of valproate throughout pregnancy cannot be excluded.

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.

If a patient becomes pregnant whilst on valproate - immediately refer to a specialist to consider alternative treatment options.
**Patients on valproate must be informed to not stop taking their treatment without advice from their specialist**.

Information for healthcare professionals:
https://uktis.org/monographs/use-of-sodium-valproate-in-pregnancy/

Information for patients:
https://www.medicinesinpregnancy.org/Medicine--pregnancy/Sodium-valproate/

**Breastfeeding:**
Valproate medicines are suitable for use in breastfeeding but the conditions of the Pregnancy Prevention Programme must be met, including that other treatments are ineffective or not tolerated.

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

Information for healthcare professionals:
- Safety in Lactation: Control of epilepsy – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice
- Treating bipolar disorder during breastfeeding – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice

**Fertility in females:**
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in females using valproate.

**Fertility in males:**
Valproate may cause infertility in men, that may be reversible after treatment is stopped or the dose is reduced in some patients.

## Paternal exposure and risk to children:

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

- A retrospective observational study has indicated a possible association between valproate use by men around the time of conception and an increased risk of neurodevelopmental disorders in their children.
- As a precaution, it is recommended that male patients use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate, to allow for one completed sperm cycle not exposed to valproate
- Male patients on valproate who are planning a family in the next year should talk to their healthcare professional about their treatment.
- If a female patient reports they are pregnant or planning a pregnancy with a man on valproate (including those undergoing IVF), refer for prenatal counselling
- Men are advised not to donate sperm during valproate treatment and for 3 months after stopping valproate.
- It is vitally important that patients do not stop taking valproate unless they are advised by their specialist to do so.

An information sheet for healthcare professionals to provide to male patients taking valproate as well as their families and caregivers is available here:
Advice_for_male_patients_on_valproate_to_use_contraception_PUBLISH_.pdf (publishing.service.gov.uk)

## Adverse effects & management:

For full details and information on ADR's and incidence, see relevant SmPC's:
http://www.medicines.org.uk/emc/

See **Table 2: 'Adverse effects and other management'** for the management of adverse effects and test results by primary care.

Report any suspected adverse drug reactions, including any case of a pregnancy exposed to valproate medicines, to the Yellow Card Scheme (see advice on reporting suspected adverse drug reactions from medicines taken during pregnancy). Should exposure occur, pregnancy outcomes should be monitored and reported.

**This list is not exhaustive. The manufacturer's summary of product characteristics (SmPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.**

## Advice to patients & carers:

The patient should 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** (this includes any vomiting or diarrhoea if taking oral contraception) or they (or their female partner, if male) may be pregnant.
- If they are **planning a pregnancy/family (male & female patients)**
- **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:**

- Use visual or other explanatory aids to support their understanding of their personalised risk of withdrawing valproate or switching to alternative treatments
- 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).
- 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:**
Sodium valproate https://www.nhs.uk/medicines/sodium-valproate/

Contraception Guide: https://www.nhs.uk/conditions/contraception/

Pregnancy prevention programme patient guide and patient card:
Valproate safety measures - GOV.UK (www.gov.uk)

MHRA: epilepsy medicines and pregnancy leaflet
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950069/Epilepsy-medicines-in-pregnancy-leaflet.pdf

## Further materials to support discussions with patients

Patients on valproate must be fully informed of the potential risks and counselled on their treatment options at the time of initial prescribing and at all subsequent reviews. We ask clinicians to use appropriate individualised language when discussing the implications of taking valproate with patients and their caregivers. The safety and educational materials should be used alongside other resources to support patients making decisions about valproate and other treatments for epilepsy and bipolar disorder. These include patient support tools, such as those published by the NHS and guidelines produced by the Association of British Neurologists.

Patient decision support tool - valproate for epilepsy:
https://www.england.nhs.uk/wp-content/uploads/2023/05/decision-support-tool-valproate-epilepsy-v1.1.pdf

Association of British Neurologists Guidelines for Valproate prescribing in Adult (16 and over) Neurology - November 2023:
https://cdn.ymaws.com/www.theabn.org/resource/resmgr/guidelines/abn_guidelines_for_valproate.pdf

## Shared Care Responsibilities

**Specialist responsibilities:**

1. Assess the patient and provide diagnosis.

2. Consider all other suitable therapeutic options before prescribing valproate. Valproate should only be initiated in patients for whom no other therapeutic options are suitable.

3. Provide an appropriate patient information leaflet and a copy of the **Prevent Patient Guide.**

4. Fulfil Specialist Prescriber responsibilities under '**Prevent – the valproate pregnancy prevention programme'**

5. Ensure female patients of childbearing potential and/or their carer understand the risks relating to pregnancy exposure to valproate.

6. Ensure male patients and/or their carer are made aware that valproate use by men around the time of conception increases the risk of neurodevelopmental disorders in their children and the recommendation to use effective contraception during valproate treatment and for at least 3 months after stopping valproate. See '**Paternal exposure and risk to children'** above. Also, discuss the risk of male infertility and testicular toxicity in animals associated with valproate therapy.

7. Use a shared decision-making approach; discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling (see also '**Advice to patients & carers'**) to enable the patient to reach an informed decision. Counselling should include **the need for highly effective contraception.** Use safety and educational materials during these discussions to support shared decision making (see also '**Further materials to support discussions with patients')**.

8. Obtain and document patient consent.

9. Assess the patient for contraindications, cautions and interactions

10. **If patient (male or female) is under 55 years, seek a second specialist (countersigning specialist)** to independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks or potential risk of testicular toxicity are not applicable.

11. Perform **baseline investigations & initial monitoring**:
    - Complete the **Annual Risk Acknowledgement Form*** *(for female patients under 55 years)*
      or **Risk Acknowledgement Form for male patients starting valproate*** *(for male patients under 55 years)*
    - Serum pregnancy test
    - Urea and electrolytes & GFR

- Full blood count
- Liver function tests, including coagulation screen
- Height, weight, and BMI

12. Liaise with or refer to primary care or sexual health service to arrange for appropriate contraception.

13. Initiate and optimise treatment with valproate. Prescribe the maintenance treatment for at least 4 weeks and until optimised.

14. Once the specialist considers the patient's condition is stable or predictable and treatment is optimised, a request can be made to the patient's GP to 'share' the patient's care.

15. Notify the patient's GP that valproate has been initiated – detailing the diagnosis, current and ongoing dose, any relevant test results and when the next monitoring is required. Include a copy of the completed Risk Acknowledgement Form, and provide contact information for the specialist team.

16. Prescribe sufficient medication to enable transfer to primary care and inform patient/carer of the arrangements for further prescriptions.

17. Conduct the scheduled **reviews and monitoring.**
    This includes:
    - Review of the clinical condition
    - Review treatment with valproate – were possible, existing patients should be switched to another treatment. Continue only if there is no other effective or tolerated treatment
    - Completion of the **Annual Risk Acknowledgement Form***.
    - Discussion regarding contraception, including a prompt to check when long-acting reversible contraceptives (e.g. implants, IUDs) must be renewed

18. As per NICE guidance, conduct regular **(at least annual)** monitoring reviews for:

    - All children and young people with epilepsy

    - Adults with epilepsy and any of the following:
      - a learning disability
      - drug-resistant epilepsy
      - a high risk of sudden unexpected death in epilepsy (SUDEP)
      - a serious comorbidity, such as complex psychosocial, cognitive or mental health problems
      - who are taking antiseizure medications associated with long-term side effects or drug interactions
      - who are able to get pregnant

19. Discussions between clinicians and patients already on valproate must include counselling on alternative treatment options and the benefits and risks associated

with any change for patients with epilepsy; this should include a discussion of the risks of sudden unexplained death in epilepsy (SUDEP).

20. After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined remains appropriate. **Provide a copy of the updated Annual Risk Acknowledgement Form to primary care.**

21. All patients will remain under the ongoing care of a named consultant/specialist.

22. The specialist will reassume prescribing responsibilities and provide advice on alternative treatment options if a patient becomes or wishes to become pregnant.

23. The specialist will provide support if problems occur using the contact details provided

24. The specialist will reassume prescribing responsibilities should any problem occur, that cannot be readily corrected in primary care.

*Two specialists (specialist prescriber and countersigning specialist) must complete and sign the appropriate Risk Acknowledgment Form:

- for new patients (male & female) under 55 years at initiation of valproate treatment.
- for existing female patients under 55 years, only at their next annual review, unless their circumstances change.

For subsequent annual reviews for female patients, only the prescribing specialist must complete and sign the Annual Risk Acknowledgement Form. The completed form should be stored in the patient's medical notes and shared with the patient and, if applicable, any healthcare professionals named on the form.

**General Practitioner responsibilities:**

1. For any new patient <55 years (male or female) where shared care of valproate is requested, ensure completed 'Annual Risk Acknowledgement Form' or 'Risk Acknowledgement Form for male patients starting valproate' is received from specialist. Confirm request includes confirmation that two specialists have independently considered and documented that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply.
   Patients restarting valproate after a period off valproate should go through the specialist service for the same confirmation and documentation, to comply with the National Patient Safet Alert.
2. For female patients of child-bearing age where shared care of valproate is requested, ensure they have a Pregnancy Prevention Plan and are on highly effective contraception unless there are compelling reasons that the reproductive risks do not apply.
3. If the Risk Acknowledgment Form or Pregnancy Prevention Plan are absent, communicate back to specialist urgently requesting this information to enable GP to take over prescribing responsibility.
4. Accept request to take on prescribing of valproate once the specialist considers a patient's condition is stable or predictable, and treatment is optimised, no sooner than 4 weeks after initiation.
5. Ensure the patient's clinical records are coded appropriately, including a code for method of contraception.
6. Ensure patient has the Patient Guide and reinforce educational points provided by the specialist. See also **'Advice to patients & carers'.**
7. For female patients of childbearing potential and/or their carers:
   - Ensure patient is using highly effective contraception and understands the need to comply with highly effective contraception throughout treatment with valproate and undergo pregnancy testing when required e.g., if there is any reason to suggest lack of compliance or lack of effectiveness of contraception.
   - Remind the patient to contact you immediately if they suspect there has been a problem with their contraception or if they may be pregnant.
   - In case of female children using valproate, remind the patient's responsible person to contact their GP once the patient using valproate experiences their first period (menarche). Their GP will refer the patient back to the specialist.
8. Remind male patients (all ages) and/or their carers that valproate use by men around the time of conception increases the risk of neurodevelopmental disorders in their children and the recommendation to use effective contraception during

valproate treatment and for at least 3 months after stopping valproate. See '**Paternal exposure and risk to children**'. Also remind patients of the risk of male infertility and testicular toxicity in animals associated with valproate therapy.

9. Remind female patients under 55 years that they will need to discuss and complete the Annual Risk Acknowledgement Form with their specialist prescriber annually.

10. Ensure the patient is given the appropriate appointments for primary care monitoring. If a patient fails to attend, contact the patient in a timely manner and arrange an alternative appointment.

11. Conduct the required monitoring as outlined below in **Table 1: General Practitioner Monitoring Responsibilities**. Communicate any abnormal results to the specialist.

12. Inform the specialist of changes in the patient's medical condition and/or prescribed medication, especially adverse effects. See **Table 2: Adverse effects and other management**

13. Refer prescribing responsibilities back to the specialist if a patient becomes pregnant or wishes to become pregnant. Advise the patient not to stop taking valproate in the interim.

14. Adjust the dose of valproate medicine prescribed as advised by the specialist.

**Migraine prophylaxis:** In patients <55 years (male or female) taking valproate for migraine prophylaxis consider gradual withdrawal of valproate over 1 month, in discussion with the patient.

Should migraines increase following cessation of valproate, seek specialist advice and guidance and, if required, refer patient into headache pathway.

15. For female patients under 55 years, ensure the patient remains under the care of the specialist, is seen by them annually for a review, and has an up to date Annual Risk Acknowledgement Form on file at all times. This should be documented in the record with the SNOMED code 1366401000000100 'Valproate Annual Risk Acknowledgement Form completed'.

16. For female patients under 55 years, put in place a robust mechanism to ensure the Annual Risk Acknowledgement Form is in date when prescriptions are issued and to ensure that patients are recalled or referred back before the expiry date. The SNOMED code 1366381000000100 'Referral for completion of Valproate Annual Risk Acknowledgement Form' can be used to document that the referral has been made. However, a prescription for sodium valproate should not be stopped simply due to a delay in specialist review/ ARAF completion, as this may put the patient at risk.

17. Refer prescribing responsibility back to the specialist should problems arise that cannot be readily corrected, this includes when the Specialist Prescriber responsibilities of 'Prevent – the valproate pregnancy prevention programme' are not being fulfilled.

MHRA and NHS Digital have advised that the SNOMED codes below are available to support primary care in accurately recording valproate annual risk assessments, part of the requirement of the national valproate alert:

- Referral for completion of Valproate Annual Risk Acknowledgement Form (procedure) SNOMED CT ID: 1366381000000107
- Valproate Annual Risk Acknowledgement form completed (situation) SNOMED CT ID:1366401000000107
- Pregnancy Prevention Programme SNOMED CT ID 1129761000000105

## Table 1: General Practitioner Monitoring Responsibilities

| Ongoing monitoring and advice (GP) | Frequency |
|---|---|
| See **Table 2: Adverse effects and other management** for the management of adverse effects and test results by primary care. | |
| • Full blood count<br>• LFT's, including prothrombin time<br>• Weight and BMI<br>Other monitoring may be required for patients with a SMI (bipolar disorder or psychosis) as part of the annual SMI health check. | Six months after initiation, and annually thereafter |
| **Annual Risk Acknowledgement Form**<br>Ensure that the patient has had an annual review with their specialist, and:<br>• an up to date annual risk acknowledgment form is on file, **or**<br>• there is a documented permanent absence of risk of pregnancy, e.g. the patient is post-menopause or has had a hysterectomy, or permanently lacks capacity to consent to sexual activity | Annually |
| **Contraception**<br>Ensure that the patient has access to an appropriate method of contraception, knows how to use it, and is 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. | At all patient contacts regarding valproate. |
| **Pregnancy testing**<br>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. | At all patient contacts regarding valproate.<br>Pregnancy testing is recommended:<br>• 3 weeks after starting a new contraceptive method, if there was any risk of pregnancy at the start of the contraceptive method<br>• Whenever there is reason to suggest lack of adherence or effectiveness of contraception<br>• More frequently in patients using a user-dependent method of contraception, e.g. condom, cap, diaphragm, oral contraceptive pills, or fertility awareness-based methods |

## Table 2: Adverse effects & other management

| Result | Action for primary care |
|---|---|
| **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** | |
| **Pregnancy confirmed** | Prescribe folic acid 5mg daily immediately, and refer to specialist and maternity/obstetrics service urgently (within days). Remind the patient not to stop taking valproate medicine in the interim. |
| **Patient planning a pregnancy** | Refer to specialist. Remind the patient not to stop using contraception or taking valproate medicine in the interim. |
| **Full blood count:**<br>Red cell count, haemoglobin or platelets below reference range | Contact specialist team for advice; consider monitoring more frequently. Do not stop valproate medicine. |
| Spontaneous bruising or bleeding, or other signs or symptoms of blood dyscrasias, e.g. purpura, sore throat, fever, or malaise | Continue valproate medicine and discuss with specialist team urgently (same day).<br>Full blood count, liver function tests, and coagulation screen are indicated; discuss most appropriate route with specialist team. |
| **Liver function tests:**<br>Raised liver enzymes in isolation | Assess clinically and review for other causes. Monitor until return to normal. Do not stop valproate medicine. Hepatic enzymes alone are not always a good measure; assess in the context of coagulation screen, albumin, and bilirubin. |
| **Signs and symptoms of liver dysfunction**, e.g.:<br><br>- prolonged prothrombin time (particularly in association with significant decrease in fibrinogen and coagulation factors, decreased albumin, increased bilirubin and raised transaminases)<br><br>- symptoms including asthenia, malaise, anorexia, lethargy, oedema, drowsiness, repeated vomiting and abdominal pain, jaundice<br><br>- recurrence of seizures | 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 |

| | |
|---|---|
| **Gastrointestinal disorders:**<br>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.<br>Do not delay admission by taking blood samples or ordering imaging in primary care. |
| **Psychiatric disorders**<br>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. |
| **Weight or BMI outside healthy range** | Do not stop valproate medicine. Provide appropriate support on multicomponent interventions to increase physical activity levels, improve eating behaviour and quality of diet.<br>Consider referral to dietician or other local services if relevant comorbidities are present (e.g. heart disease, diabetes) or BMI >35. |

**Patient and/or carer responsibilities:**

- Read and keep the Patient Information Leaflet and Patient Guide, discuss and complete the appropriate Risk Acknowledgement Form with their specialist.
- Take valproate medicines as prescribed and avoid abrupt withdrawal unless advised by the primary care prescriber or specialist.
- Attend regularly for monitoring and review appointments with primary care prescriber and the specialist. Keep contact details up to date with both prescribers. Be aware that medicines may be stopped if they do not attend.
- If female and under 55 years, attend annual review with specialist to discuss and complete the Annual Risk Acknowledgement Form.
- Report adverse effects to their primary care prescriber. Seek immediate medical attention if they develop any symptoms as detailed in ‘Advice to patients & carers’
- Patients of child-bearing potential should use an appropriate form of contraception, as agreed with their doctor/nurse/sexual health service.
- Patients of childbearing potential should take a pregnancy test if they think they could be pregnant, and inform the specialist or GP immediately if they become pregnant or wish to become pregnant.
- Male patients of any age should not donate sperm during valproate treatment and for 3 months after stopping valproate
- Not to stop taking valproate without advice from a healthcare professional.
- Report the use of any over the counter medications to their primary care prescriber and specialist, and be aware they should discuss the use of valproate medicines with their pharmacist before purchasing any OTC medicines.
- Alcohol intake is not recommended during treatment with valproate. Avoid recreational drugs.
- Not to drive or operate heavy machinery if valproate affects their ability to do so safely. If unsure, talk to their doctor, pharmacist or healthcare professional.

## Further support

- Contact specialist team via agreed channels.
- Prescribing & Medicines Management Team, NHS Somerset ICB
  Tel: 01935 384123  Email: somicb.medicinesmanagementteam@nhs.net

| Version: | V1.1 | Date |
|---|---|---|
| V1.0 Drawn up by: | Hels Bennett, Medicines Manager, NHS Somerset ICB<br>Draft V0.5 updated to V1.0 following approval at MPB Feb 2024 | February 2024 |
| V1.1 updated by: | Hels Bennett, Medicines Manager, NHS Somerset ICB<br>Updated following MHRA alert **Valproate use in men: as a precaution, men and their partners should use effective contraception.** Published 5 September 2024.<br><br>Title & contents updated to include all patients on valproate. Ethical considerations section condensed. NICE guidance on frequency of reviews added. Further support section updated.<br><br>Updated version noted at MPB Nov 2024 | October 2024 |
| V1.2 | Updated NICE guidance published NG217 Epilepsies in children, young people and adults Published: 27 April 2022 Last updated: 30 January 2025 – links and references updated. | 30.01.2025 |
| V1.3 | Updated following MHRA Drug Safety Update **Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): review by two specialists is required for initiating valproate but not for male patients already taking valproate** Published 13 Feb 2025<br><br>Information and infographics added to Introduction section. | 25.03.2025 |
| Approved by: | NHS Somerset Medicines Programme Board (MPB) | 28.02.2024 |
| | Drug & Therapeutics Committee, Somerset NHS FT | |
| | MH Drug & Therapeutics Committee, Somerset NHS FT | |
| | | |
| Review by: | | January 2026 |

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