MIL

Oxford University Hospitals NHS
NHS Foundation Trust

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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Oral Valproate - FEMALE patients under the age of 55 years and MALE patients

This MIL provides prescribing and monitoring guidance for oral valproate (valproic acid, sodium valproate, or valproate semi-sodium) therapy in all patients (male and female) under the age of 55 years and males 55 years and older who have the potential to father a child. This MIL should be read in conjunction with:

1. Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc
2. Health Care Professionals guide within the risk materials provided by the manufacturer
3. BNF or BNFC, available on https://bnf.nice.org.uk/

Key points

- **Females**: Exposure to valproate in pregnancy is associated with physical birth defects in 11% of babies and neurodevelopmental disorders in up to 30-40% of children, which may lead to permanent disability.[1]
- **Males:** Registry data suggests an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception. In the study, around 5 children in 100 born to fathers treated with valproate around conception were diagnosed with a neurodevelopmental disorder. This is compared to 3 in 100 children whose fathers were taking lamotrigine or levetiracetam around conception.[1]

Full Regulatory Safety and Educational Materials can be accessed here:

Valproate safety measures - GOV.UK

The Medicines and Healthcare Regulatory Agency (MHRA) stipulates mandatory regulatory measures to reduce the known harms of valproate. A summary is below; further information is overleaf:

- Oral valproate must NOT be started in new patients (male or female) younger than 55 years and males 55 years and older who have the potential to father a child, unless two specialists (consultant neurologists or consultants in psychological medicine) 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 most patients, other effective treatment options are available.
- **Prescribing** → continue to prescribe valproate for existing patients and if required offer patients a referral to a specialist to discuss their treatment options.
- **Dispensing** → dispense in the manufacturer's original full pack.
- **Long-term prescribing and monitoring** → manage via BOB ICB shared care protocol (Oral Valproate Medicines Shared Care Protocol for all Patients (male and female) under the age of 55 and those over 55 who are planning to have children).

Incident reporting

Report incidents of harm or near miss via Ulysses and MHRA yellow card reporting (https://yellowcard.mhra.gov.uk/)

Initiation of treatment

For ALL patients (male and female) under the age of 55 years and MALES wo are 55 years and older who have the potential to father a child, and require initiation of treatment with oral valproate:

1. Oral valproate should be initiated by a specialist.
2. A second specialist must agree that this is the most appropriate treatment at initiation and sign the Annual Risk Acknowledgement Form (**females only**) OR a risk acknowledgement form for male patients starting valproate (**males only**).

Female patients MUST be reviewed by a specialist at least annually and an Annual Risk Acknowledgement Form completed.

Q. What if oral valproate is initiated by a specialist during admission to hospital?

- Two specialists must complete risk acknowledgement documentation as above.

Q. What if INTRAVENOUS sodium valproate is initiated as an emergency during a hospital admission?

- The MHRA drug safety update only covers **ORAL** valproate. Intravenous (IV) valproate may be initiated as per Guidelines for the Management of Generalised Status Epilepticus in Adults (sharepoint.com) or following advice from neurology.
- When reviewing the ongoing need for sodium valproate, consider switching to an alternative (or stopping), under the guidance of the neurology team. If a decision is made to continue valproate, the patient MUST be reviewed by a specialist prior to switching to from IV to oral valproate.
- The Annual Risk Acknowledgement Form (**females only**) OR a risk acknowledgement form for male patients starting valproate (**males only**) must be completed and copy forwarded to the GP. A copy should be given to the patient and a copy placed on EPR in the patient record.

Continuation of treatment

Q. What if a patient has been taking oral valproate prior to hospital admission?

Continue to prescribe and supply valproate. For patients with a history of seizures, abrupt withdrawal of valproate may lead to uncontrolled seizures. If a review of epilepsy medication is required, please discuss treatment options with the neurology liaison team.

Contacts

Neurology liaison registrar: Consult referral via EPR
Neurosciences pharmacy team: NeurosciencePharmacyTeam@oxnet.nhs.uk

Further risk management materials available

For HCPs Dispensary poster I Warning Stickers I HCP information on the risks of valproate use in all patients

For patients Product Information leaflet I Patient guide for women I Patient card I Valproate guide for male patients

Summary of Risk Acknowledgement Documentation

	When	Who	What
Females and people of childbearing potential	When initiating oral valproate **OR** 1st annual review after publication of valproate drug safety update 2024.	Specialist	Patients must be reviewed using the valproate Annual Risk Acknowledgement Form. A second specialist signature is required if the patient is to continue valproate.
	Subsequent annual reviews	Specialist	Patients must be reviewed using the valproate Annual Risk Acknowledgement Form Only one specialist's signature is required, unless the patient's circumstances have changed.
Females with a permanent reason for non-childbearing potential	When initiating oral valproate	Specialist	Patients must be reviewed using the valproate Annual Risk Acknowledgement Form. There is no need to complete the form beyond step1.
Males who have the potential to father a child	When initiating oral valproate.	Specialist	A risk acknowledgement form for male patients starting valproate (RAF) must be used to support and record the discussion between the patient and specialist prescriber about the risks associated with valproate, and to record the decision of the countersigning specialist. Valproate guide for male patients

Short summary of pharmacy dispensing guidance:

- Full packs of oral sodium valproate and valproic acid (as valproate semisodium) must be supplied, including for stock, inpatients, outpatients, and discharge.
- The only exception is dispensing dosette boxes / multi-compartment compliance aids on discharge.
- Where an excess quantity will be supplied to patients e.g. tapering courses or changing doses, the label must include the statement 'please discard unused medicines safely at a pharmacy after completing the course of treatment.
- Split packs will not be available in any dispensaries; any used or split packs e.g. returned from clinical areas or left over from dosette box dispensing should be discarded in blue lidded waste bins in dispensaries.
- Patient Information Leaflet must be supplied with valproate-containing medicines in a dosette box.

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