Association of British Neurologists

Guidelines for Valproate

The MHRA and CHM have issued new recommendations regarding valproate for **anyone under the age of 55 with reproductive capacity** (https://www.gov.uk/drug-device-alerts/national-patient-safety-alert-valproate-organisations-to-prepare-for-new-regulatory-measures-for-oversight-of-prescribing-to-new-patients-and-existing-female-patients-natpsa-slash-2023-slash-013-slash-mhra). Most of below applies to oral valproate use in people with epilepsy; valproate is used for migraine although is not licensed for this indication. Although this guidance refers specifically to valproate, **TOPIRAMATE** is also teratogenic (https://www.gov.uk/drug-safety-update/topiramate-topamax-start-of-safety-review-triggered-by-a-study-reporting-an-increased-risk-of-neurodevelopmental-disabilities-in-children-with-prenatal-exposure). There are two phases for the implementation of these new valproate recommendations:

- **Phase 1 (January 2024)** applies to all new start valproate prescribing for men or women **AND** all current valproate prescribing for women (i.e. women already on valproate).
- **Phase 2 (date to be announced)** will apply to all men currently prescribed valproate.

These ABN guidelines address Phase 1 implementation only, as follows:

Starting valproate (as of 31.1.24): no one under the age of 55 should be started on valproate unless two specialists (defined below) independently consider and document that there is no other "effective or tolerated" treatment, or there are compelling reasons why the reproductive risks do not apply.

Women under 55 already on valproate (as of 31.1.24): At their next scheduled review, two specialists are required to independently consider and document that there is no other effective or tolerated treatment.

Specialist/accepted signatories are defined by MHRA/CHM as:

- Consultant neurologist (at least one signatory on the two signatory forms must be a Consultant)
- Associate specialist/specialty doctor in epilepsy/neurology
- Epilepsy specialist nurse

The issue of valproate teratogenicity in women is well recognised and the Pregnancy Prevention Programme has been in place since 2018. For men, there is a risk of likely reversible infertility; there are also concerns of "testicular toxicity" although further evaluation is required.

November 2023. Review: November 2028.

The ABN recognises this will be a difficult period for people taking valproate, neurologists, and neurology services. We recommend working closely with your Integrated Care Board (England), Health Board (Scotland and Wales), and Health and Social Care Trusts (Northen Ireland). As neurologists, we must recognise and adopt the new regulatory framework, balancing the risk from seizures with the reproductive risk from medication. We must ensure patients are well informed regarding these risks, to allow them to make appropriate decisions. Valproate can, with appropriate counselling and documentation, still be used. Working within these new recommendations should ensure that valproate remains available for those who need it.

Phase 1 implementation

People who require two specialist signatures/agreement

- All people (men and women) starting valproate from 31.1.24 will need two specialist signatures **once** on the new risk acknowledgement form (RAF); thereafter annual review and annual risk acknowledgement form (ARAF) completion with a single signature is required for **women only**.
- All women already on valproate will need two specialist signatures **once** at the next scheduled review; thereafter annual review and ARAF completion with a single signature is required.

  Men currently prescribed valproate are **not** included in Phase 1.

Obtaining and documenting two specialist agreement

From 31.1.24, a second independent specialist will need to agree that there are no other effective or tolerated treatment options to prescribing valproate.

- The MHRA/CHM has defined "specialist" as a consultant neurologist, specialty doctor/associate specialist in epilepsy/neurology, or epilepsy specialist nurse. At least one of the signatories on the two signatory risk acknowledgement forms must be a consultant neurologist.
- A review of case notes or case discussion within an MDT framework may be used to obtain second signatures; face to face review by the second specialist is not specifically required. A specimen MDT form will be available on the ABN website.
- The risk acknowledgement forms remain paper or PDF based; the MHRA will provide updated forms upon introduction of the first phase. A wet ink signature is not required, forms may be completed/signed electronically on the PDF version. It is hoped digital forms will be provided soon.
- Once two signatures have been obtained, all women continuing valproate must be reviewed annually (in line with the current PPP guidelines) to confirm that valproate remains the most suitable treatment (i.e. there is no other effective or tolerated treatment) by completion of the ARAF by a single

specialist. All prescribing decisions should occur under the guidance/care of a Consultant Neurologist.

- For women already treated with valproate, review by a second signatory may be deferred until the next scheduled review. Once the second signature is obtained, subsequent annual review/ARAF requires a single signature.

Alternatives to valproate:

Epilepsy

Although valproate may be the most effective treatment for some idiopathic (genetic) generalised epilepsies, there are alternatives. Lamotrigine or Levetiracetam are usually the appropriate first line choices as an alternative to valproate. NICE guidance currently recommends valproate as first choice for IGE/GGE but we anticipate this guidance will be updated to reflect the new regulations.

https://www.sign.ac.uk/media/1079/sign143_2018.pdf

https://www.nice.org.uk/guidance/ng217

https://www.gov.uk/drug-safety-update/antiepileptic-drugs-in-pregnancy-updated-advice-following-comprehensive-safety-review

Migraine: valproate is not licensed for use in migraine and there are many alternatives although some (such as topiramate) also have teratogenic risks.

https://www.bash.org.uk/guidelines/

https://www.nice.org.uk/guidance/cg150/evidence/full-guideline-pdf-188258224

https://www.sign.ac.uk/our-guidelines/pharmacological-management-of-migraine/

Other useful sources of information

- MHRA valproate information page: https://www.gov.uk/government/collections/valproate-safety-measures

FSRH CEU guidance: Drug interactions with hormonal contraception

https://www.fsrh.org/documents/ceu-clinical-guidance-drug-interactions-with-hormonal/

FSRH CEU Statement: Contraception for women using known teratogenic drugs or drugs with potential teratogenic effects.

https://www.fsrh.org/documents/fsrh-ceu-statement-contraception-for-women-using-known/

Public Assessment Report
(https://www.gov.uk/government/publications/valproate-review-of-safety-data-and-expert-advice-on-management-of-risks)

FAQs

What do I need to do now? Familiarise yourself with the National Patient Safety Alert, Public Assessment Report, and this guideline. No immediate clinical action is needed, these new recommendations (phase 1) will apply 31.1.24.

What led to these new regulations? Although the teratogenic effects of valproate for women have been known for many years and the Pregnancy Prevention Programme was introduced in 2018, the MHRA has been concerned that pregnancies are still occurring in women taking valproate and that women remain unaware of the risk of valproate when taken during pregnancy. New data from animals have shown "testicular toxicity" in juvenile and adult males and although there is a known risk of infertility in men, the impact of these data is currently unknown. Animal reproductive toxicity studies have shown that valproate exposure can lead to the transmission of behavioural abnormalities through to the third generation. Epigenetic effects of valproate on the male and female germ cell are being investigated in an ongoing study and an expert working group of the CHM has been established to advise on the potential epigenetic mechanisms of valproate. In addition, the possible risk of neurodevelopmental disorders in children whose fathers were exposed to valproate is being evaluated by the MHRA/CHM and we await their recommendations.

What are the specific new risks to convey to men? Men should be made aware of the potential risk of infertility with valproate and should also be made aware that animal studies have shown a spectrum of reproductive toxicities across different mammalian species. The CHM will evaluate a post authorisation safety study highlighting increased risks of neurodevelopmental disorders in children of males exposed to valproate (Safety of valproate – new study on risks in children of men taking valproate - GOV.UK (www.gov.uk)). The outcome of this study, together with regulatory actions for men already on valproate will be communicated as soon as possible. The MHRA have also released a Public Assessment Report containing more detail.

Do the new regulations apply to all patients? No, the new guidance is aimed at people aged up to 55 with reproductive capacity. Although 55 years is the upper age limit specified by the MHRA, if you believe that a man or woman over 55 have reproductive capacity, you should consider the new guidance relevant in making decisions, although you would not need to complete a risk acknowledgement form.

Do men up to 55 who are already on valproate need review? No, not presently, although in due course, new regulations for this group will be published (phase 2).

Are there new Risk Acknowledgement Forms? Yes, these will be made available via the MHRA website in due course
https://www.gov.uk/government/collections/valproate-safety-measures

Are the new forms digital? No, they are available as paper or PDF versions. The ABN have advocated that digital forms should be introduced.

Are two signatories required every year? No, two signatories are only required when people are started on valproate. Thereafter, only one annual signatory is needed for women only. Women who are currently taking valproate also require two signatories on one occasion, obtained at their next scheduled review.

Who is eligible as a signatory? Consultant neurologists, associate specialists/specialty doctors in epilepsy/neurology, and epilepsy specialist nurses are permitted signatories. Neurologists in training and GPs are not permitted signatories. At least one of the dual signatories on the RAF must be a consultant neurologist.

What advice is being provided to GPs/primary care? GPs will be advised to continue prescribing valproate, but to refer any women up to 55 with reproductive capacity prescribed valproate who are **not** presently under regular secondary care review.

Are the NICE guidelines going to be updated? After the initial MHRA recommendations were published in December 2022, NICE indicated that the valproate recommendations in the guideline will be reviewed once further advice from the MHRA is available.

Will I receive more resource to satisfy these new regulations? No, the ABN are not aware of any new resources that will be made available.

What about patient choice? Sensible and responsible prescribing takes account of current regulatory frameworks (including licensing criteria) as well as patient choice/preference. Our responsibility is to ensure that all people prescribed valproate are aware of the information now available and are thus able to make informed choices about their treatment. Valproate is still available for prescription and for some people under 55 years of age, it will remain the best treatment.

What if the second prescriber disagrees with the decision to start or continue valproate? The reasons should be discussed with the patient. The patient may wish to discuss further with the second prescriber to explore these concerns. Shared decision making and informed risk: benefit balancing is essential. The patient's informed final preference should be respected, patients should not be taken off valproate against their wishes. The patient should sign the Risk Acknowledgement Form.

What if I can't find a second prescriber and want to start valproate urgently? Valproate can be prescribed in this scenario but would be considered off-label until a second signature is obtained, and extra care should be taken (see GMC off-label guidance).

Does this guidance include IV valproate use in status epilepticus? No, this refers to oral valproate only. Preservation of life is the primary goal in status management, you should refer to your own hospital protocols for status management.