National Patient Safety Alert

Medicines & Healthcare products Regulatory Agency

Valproate: organisations to prepare for new regulatory measures for oversight of prescribing to new patients and existing female patients

Date of Issue:	28 November 2023	Reference No:	NatPSA/2023/013/MHRA

This alert is for action by: Integrated Care Boards (in England), Health Boards (in Scotland), Health Boards (in Wales), and Health and Social Care Trusts (in Northern Ireland)

This is a safety critical and complex National Patient Safety Alert. Implementation should be coordinated by an executive lead for quality (or equivalent) in Integrated Care Boards in England, Health Boards in Scotland, Health Boards in Wales, and Health and Social Care Trusts in Northern Ireland, alongside the Chief Pharmacist (or equivalent) and supported by the Medical Directors of organisations involved in the prescribing of valproate and clinical leads in neurology, psychiatry, paediatrics, learning disability and/or autism, contraception and sexual health, and general practice, with others included to meet local needs and clinical situations.

Explanation of identified safety issue:

The MHRA is asking organisations to put a plan in place to implement **new regulatory measures** for sodium valproate, valproic acid and valproate semisodium (valproate). This follows a comprehensive review of safety data, advice from the Commission on Human Medicines and an expert group, and liaison with clinicians and organisations.

Due to the known significant risk of serious harm to a baby after exposure to valproate in pregnancy, these measures aim to ensure valproate is only used if other treatments are ineffective or not tolerated, and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme (PPP). Given these and other risks of valproate, these measures also aim to reduce initiation of valproate to only in patients for whom no other therapeutic options are suitable.

The regulatory change in January 2024, for oral valproate medicines, means that:

A. 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.

B. 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

Advise leaders that current safety measures for valproate continue to apply, including the valproate PPP for any girls and women of childbearing potential. See December 2022 Drug Safety Update for further information, including advice for clinicians to consider all other suitable therapeutic options before newly prescribing valproate in patients younger than 55.

Advise leaders in general practice and pharmacy that teams should continue to prescribe and dispense valproate but also discuss the current warnings and upcoming measures relating to valproate with their patients and consider together how it affects the patient's individual circumstances. New educational materials should be integrated into local guidance to ensure patients are able to make an informed choice.

Actions required

When: To begin as soon as possible and be completed by **31 January 2024**

1. Designate a new or existing group to co-ordinate the implementation of the new regulatory measures in providers, with oversight from a senior quality group. This group should include (but is not restricted to):
   a. An appointed chair with delegated responsibility for the actions in this alert.
   b. Representation from clinical leads in all the specialities named above and any other relevant departments.
   c. A mechanism by which the group can involve and be informed by patients with lived experience.

2. The group should be tasked with, and document, progress towards:
   a. Updating all local guidance and protocols relating to prescribing of valproate to reflect the new regulatory position, including definitions of the roles and responsibilities of clinicians and provider organisations, and the recording of compliance with the risk forms
   b. Commissioning work if necessary to understand the needs of the affected population, including those people most at risk of health inequalities.
   c. Reviewing the results of local audit(s) of compliance with the existing PPP measures for girls and women of childbearing potential prescribed valproate.
   d. Commissioning/determining the local pathways of care for women of childbearing potential and girls in relation to the prescribing and review of valproate.
   e. Planning for and identification of clinical resource to meet the identified needs of the population and implement the new regulatory measures.

3. Based upon the findings of the above, the group should produce an Action and Improvement Plan by the alert deadline that is communicated with all relevant staff to ensure smooth implementation of the new regulatory measures and to allow for continuous improvement in care of patients who are considering or being prescribed valproate, including ongoing improvement, monitoring and audit.

Additional information:

Safety concerns and latest data

Patients on valproate must be informed to not stop taking their treatment without advice from their specialist.
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. Since 2018, valproate has been contraindicated in women of childbearing potential unless the PPP is in place.

In 2022, the Commission on Human Medicines (CHM) reviewed the latest data on the safety of valproate. The CHM heard from patients and other representatives on their views about how valproate was being used and how the risks were currently managed. The CHM noted that data from the Medicines and Pregnancy Registry show pregnancies in England continue to be exposed to valproate. The CHM also considered other known risks of valproate, including the risk of impaired male fertility. The CHM considered pre-clinical data on possible transgenerational risks with prenatal exposure, as well as data from studies in juvenile and adult animals suggesting adverse effects on the testes. There is currently limited data available on many of these risks in humans and further studies are planned. However, the CHM noted many patients receiving valproate have other therapeutic options with fewer reproductive potential harms.

The MHRA announced the recommendations of the CHM in December 2022 and has taken advice from CHM and an expert advisory group. A list is provided online of roles that could fulfil the second signatory. These individuals should not be in direct line management of the primary signatory. Multidisciplinary Teams (MDTs) could be used to discuss and agree a prescribing decision, with the second signatory being a representative of the MDT who meets the criteria for a specialist signatory. The details of the two signatories should be recorded in the Risk Acknowledgement Forms for female and male patients under the age of 55. Further clinical guidance is available.

The regulatory change and associated educational materials to support patients and healthcare professionals will be published on the MHRA website when available. Where appropriate, additional recommendations are expected later in 2024 in relation to review of men under 55 years of age on valproate. Until these are published, men under 55 on valproate are advised to read the Patient Information Leaflet and should be given the opportunity to discuss concerns with their GP and if required, offered a referral to a specialist to discuss their treatment options.

See the MHRA Public Assessment Report and MHRA website, which will be added to in the coming weeks and months. The MHRA review of antiepileptic drugs in pregnancy should also be consulted.

Stakeholder engagement:
This action has been endorsed by the CHM. In formulating this position, the CHM considered the perspectives and views of patient groups and public and healthcare professional stakeholders.

On this alert we engaged with representatives from NHS England, and representatives from the Scottish Government, Welsh Government, and Northern Ireland, CQC, GMC, GPhC, and members of the Association of British Neurologists.

Advice for Central Alerting System (CAS) officers and risk managers
This is a safety critical and complex National Patient Safety Alert. In response to CHT/2023/002 your organisation should have developed processes to ensure appropriate oversight and co-ordination of all National Patient Safety Alerts. CAS officers should send this Alert to executive lead nominated in their new process to coordinate implementation of safety critical and complex National Patient Safety Alerts, copying in the leads identified on page 1.

NHS England

Department of Health www.health-ni.gov.uk

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