Medicines & Healthcare products Regulatory Agency

Valproate: regulatory update

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Public Assessment Report

- MHRA published a Public Assessment Report in November 2023
- This provides an overview of the data considered by the Commission on Human Medicines (CHM) and its Expert Working Group
  - It includes all medicines containing valproate for the approved indications in Epilepsy and Bipolar disorder
  - Outlines the reasons the review was undertaken
  - How CHM reached their conclusions
  - The CHM's recommendations
  - CHM's implementation recommendations

- Reinforces the message that patient should not stop taking valproate without advice from a specialist

National Patient Safety Alert

- National Patient Safety Alert issued on 28 November 2023
- Instructed healthcare organisations to put in place a plan to implement the first phase of the new regulatory measures for valproate by 31 January 2024

This outlined that from January 2024:

- 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.
- All women who could become pregnant and girls who are currently taking valproate should be reviewed by two specialists at their next annual specialist review
  - Completing a revised valproate Annual Risk Acknowledgement Form

Regulatory changes

- The Commission on Human Medicines recommendations for greater clinical oversight of valproate have been incorporated into the terms of the licenses for valproate containing medicines.
- The following have been updated:
  - Summary of Product Characteristics (SmPC)
  - Patient Information Leaflets (PIL)
  - Patient Guide
  - Healthcare Professional Guide
  - Pharmacy poster
  - Patient Card
  - Annual Risk Acknowledgement Form for female patients
- A new Risk Acknowledgement Form for male patients starting valproate was developed

Valproate containing medicines

- Any medicine containing the active ingredient valproate as:
  - sodium valproate
  - valproic acid
  - valproate semisodium

- Brands include:
  - Epilim, Depakote, Convulex, Episenta, Epival, Syonell, Belvo & Dyzantil
  - Generic sodium valproate

- The requirement for two specialists applies to oral formulations only

Summary of Product Characteristics

- Change to sections:
  - 4.1 - Therapeutic indications
  - 4.2 - Posology and method of administration
  - 4.3 - Contraindications
  - 4.4 - Special warnings and precautions for use
  - 4.6 - Fertility, pregnancy and lactation
  - 4.8 - Undesirable effects

- Available online on MHRA website or electronic medicines compendium

Patient Information Leaflets (PIL)

- The PIL reflect the SmPC
- Currently available online on MHRA website or electronic medicines compendium
- Updated PILs will be included in new packs and will enter the pharmacy chain in 3-6 months
- Some PILs currently in packs, include a QR code which links patients to the new patient documents online including the new PIL

Risk materials

- The risk minimisation materials or educational materials include:
  - Patient Guide
  - Healthcare Professional Guide
  - Pharmacy poster
  - Patient Card
  - Annual Risk Acknowledgement Form for female patients
  - Risk Acknowledgement Form for male patients starting valproate
- Produced by the Marketing Authorisation Holders and content is approved by MHRA
- A single set of documents have been approved to be used for all valproate containing medicines
- Only available in English
- Currently available online on MHRA website or electronic medicines compendium
- Distribution of paper copies of the documents began on 5 February 2024

Patient Guide

- The Patient Guide (dated December 2023) has been updated to include:
  - The requirements for new patients
  - Updated advice for female patients
  - Information for male patients

- Reminds patients to also read the PIL
- Reminds patient not to stop taking valproate unless advised by a specialist

Healthcare Professional Guide

- The Healthcare Professional Guide (dated December 2023) includes:
  - An outline of the purpose of the guide
  - Highlights what's new
- Outlines actions for:
  - General Practitioners, Specialist Prescribers and Pharmacists
  - Female and male patients
- Does not define who is classified as a specialist prescriber
  - This is addressed in the Public Assessment Report and clinical guidance
  - Allows some flexibility at a local level

Pharmacy poster

- The Pharmacy poster (dated December 2023) replaces the previous poster
- It outlines the important actions for pharmacists including:
  - Provision of the new patient card to female patients
  - Checking the patient has received the Patient Guide or knows how to access it online
  - Confirming female patients are aware of the risks and the need to use contraception
  - Dispensing valproate in its original packaging

- Pharmacists do not need to verify a risk acknowledgement form has been completed before dispensing valproate

Patient Card

- The updated Patient Card (dated December 2023) contains information for female patients
- Pharmacists should have received packs containing new patient cards
- These new cards replace the existing cards provided on or in packs of valproate
  - As an interim measure, until the updated packs with the new card are in the pharmacy chain, pharmacists should remove the existing patient card from the pack and provide female patients with the new card

Annual Risk Acknowledgement Form for female patients

- The Annual Risk Acknowledgement Form for female patients (dated December 2023) replaces the existing ARAF
- The new form should be completed by two specialists for all females under 55 years starting valproate
- The new form should also be completed by two specialists for female patients under 55 years at their next annual review, thereafter one specialist can complete the form
- Stakeholder feedback has been incorporated in the updated ARAF:
  - It’s an editable pdf that can be used within some software systems or to support remote appointments
  - Wet signatures are not required
  - There is now a clear space to record why the pregnancy prevention programme may not apply
  - The form is dated on completion but does not have an expiry date

Risk Acknowledgement Form for male patients starting valproate

- The Risk Acknowledgement Form for males starting valproate (dated December 2023) ensures they are aware of the reproductive risks before starting treatment
- This is completed with the patient when valproate is being started
- There is currently no requirement for specialists to review male patients annually or complete this form more than once
- The form focuses on the risks of male infertility and testicular toxicity as although there had been warnings in the product information for many years there is very low awareness of these risks

Study examining risk in children of men taking valproate

- The MHRA has kept under close review the possibility of risks to children associated with paternal exposure to valproate
- The study report submitted to the MHRA and to other regulatory authorities suggests that children whose fathers took valproate during the 3-month period before they were conceived had a small increased risk of neurodevelopmental disorders compared to children whose fathers had taken other antiseizure medicines such as lamotrigine or levetiracetam
- However, we were subsequently informed of errors that may have impacted on the results
- A full re-analysis has been undertaken and independent advice sought from our advisory committees
- Recommendations associated with the paternal risk will be communicated soon

Next Steps

- We are monitoring the impact of the new regulatory requirements
- The second phase of implementation will take into account the impact of the initial phase and the new data on risks for male patients and their offspring

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