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Dear Claire

FURTHER REGULATORY MEASURES FOR VALPROATE

You may be aware that the Medicines and Healthcare products Regulatory Agency (MHRA) issued a UK-wide National Patient Safety Alert (NatPSA) on 28 November 2023 to communicate the further regulatory measures for valproate (a medicines which is approved in the UK to treat epilepsy and bipolar disorder but can cause birth defects and neurodevelopmental disorders following use in pregnancy). I thought it would be helpful to provide the committee with some context and next steps for this work.

The NatPSA which was issued on 28 November 2023 by the MHRA states that, from 31 January 2024:

- Valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently agree and document that there is no other effective and tolerated treatment.
- At their next annual specialist review, female patients of childbearing potential and girls should be reviewed using the latest valproate Acknowledgement of Risk Form, which will include the need for a second signatory if the patient is to continue with valproate.

This is a safety critical and complex NatPSA. Implementation of the actions will be coordinated by an executive lead for quality (or equivalent) in Health Boards in Scotland, alongside the Director of Pharmacy 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 & sexual health, and general practice, with others included to meet local needs.

The Chief Pharmaceutical Officer (CPO) issued a letter on 28 November 2023, alongside the NatPSA to highlight the regulatory changes and to note the work of the Scottish Government Teratogenic Medicines Advisory Group, which the CPO chairs, and the Anti-Seizure Medicines Task and Finish Group, chaired by the Director of Pharmacy, NHS Forth Valley.

Context

Valproate (brand names Epilim®, Depakote ®) is authorised for the treatment of epilepsy and bipolar disorder. Licensed in 1972, it is known to be teratogenic and when used in pregnancy is associated with an 11% risk of major birth defects and 30-40% risk of neurodevelopmental disorders, which may cause permanent disability in children. There is emerging evidence of adverse reproductive effects in males.

In December 2022, the MHRA announced the recommendations of the Commission on Human Medicines (CHM) for additional measures to reduce the harms from valproate considering all available data. These measures included that no new patients under 55 years of age should start valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment or the reproductive risks do not apply and that healthcare professionals should consider switching patients of reproductive potential from valproate if it is safe to do so. All women remaining on valproate must continue to follow the requirements of a Pregnancy Prevention Programme. A Valproate Implementation Expert Working Group of the CHM met multiple times to discuss and advise on the safe introduction of the new measures across the healthcare system. The CPO is a member of the Expert Working Group.

At their meeting of 29 June 2023, the CHM advised that the MHRA should proceed with the phased implementation of the recommendations of December 2022 for all patients under 55 years of age newly prescribed valproate and the prevalent female population. For men currently taking valproate the requirement for the “two specialists” review will begin in a later phase (phase 2), incorporating advice from healthcare professionals and patients developed considering experience with the initial phase.

Phase 2 – Re-analysis of paternal risk data

The MHRA identified the need for reanalysis of a new study that showed an increased risk of neurodevelopmental disorders (NDDs) in children when the father took valproate compared with other anti-epileptic treatments.

The updated study data have been received by the MHRA and other regulators across Europe. The data are currently being considered and advice will be sought from the CHM and relevant advisory committees in January 2024. The data will also be assessed within Europe by the Pharmacovigilance Risk Assessment Committee which is currently expected to publish its recommendations on 12 January 2024.

Next steps

The Scottish Government Anti-Seizure Medicines Task and Finish Group is drafting a consensus statement on the prescribing of Valproate for people of childbearing potential (anyone who may be able to get pregnant up to the age of 55 years old) that will be sent to all Health Boards in Scotland to ensure consistency in messaging.

My officials are engaging with the MHRA on phase 2 and will provide a further update on this in early 2024 once further information is available.

I hope that this update to the Committee is helpful.

Yours sincerely,

JENNI MINTO

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