Ministear airson Slàinte Phoblach is Slàinte Bhoireannach
Jenni Minto BPA

Minister for Public Health and Women's Health
Jenni Minto MSP

T: 0300 244 4000
E: scottish.ministers@gov.scot

Scottish Government
Riaghaltas na h-Alba
gov.scot

Clare Haughey MSP
Convener
Health, Social Care and Sport Committee
The Scottish Parliament

hscs.committee@parliament.scot

9 September 2024

Dear Clare,

**FURTHER REGULATORY MEASURES FOR VALPROATE USE IN MEN**

On 14 December 2023, I wrote to you to provide an update on the Medicines and Healthcare products Regulatory Agency (MHRA) further regulatory measures for valproate use in all patients under 55 years of age (female and male) from 31 January 2024. In that correspondence, I noted that I would provide a further update on phase 2 of this work in relation to paternal risk data.

The MHRA published a Drug Safety Update (DSU) for valproate use in men on 5 September 2024. The new advice provided by the MHRA in the DSU is in addition to the measures introduced in January 2024. The DSU on valproate paternal risk can be accessed online at: Valproate use in men: as a precaution, men and their partners should use effective contraception - GOV.UK (www.gov.uk).

The MHRA's final analysis of results of a retrospective observational study indicates a possible association between valproate use by men around the time of conception and an increased risk of neurodevelopmental disorders in their children. The DSU notes that male patients of reproductive potential should be informed of this potential risk at initiation and at their next treatment review. As a precautionary measure, it is recommended that male patients and their female partner should use effective contraception during valproate use and for at least 3 months after stopping valproate. The DSU highlights that patients should not stop taking valproate without discussing this with their healthcare professional.

## Context

During the 2018 European review into the risks of valproate in pregnancy, a number of concerns were considered about risks in all patient groups, including the potential risks to children born to fathers who take valproate. More information on the evidence assessed at that time is available in the assessment report by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency. A retrospective observational study was requested by the European regulatory authority to examine any association between exposure to valproate in men and the risk of congenital abnormalities and developmental disorders, including Autism Spectrum Disorder, in their offspring. The findings of the study were received by the MHRA in January 2023, and the Commission on Human Medicines (CHM) considered these, however, subsequently, the MHRA was notified of errors in the data provided by the manufacturers, and a reanalysis of the study results was requested. The reanalysis was reviewed by the Pharmacovigilance Expert Advisory Group (PEAG) and the CHM in February 2024.

## Topiramate

In addition to providing an update on valproate, I also wish to update you on the MHRA's recent introduction of new safety measures for topiramate, which is used for migraine prevention and to treat epilepsy. The MHRA published a DSU for topiramate on 11 June 2024, so that topiramate is now contraindicated in pregnancy and in women of childbearing potential unless the conditions of a Pregnancy Prevention Programme are fulfilled. This follows a review by the MHRA which concluded that the use of topiramate during pregnancy is associated with significant harm to the unborn child. The topiramate DSU can be accessed online at: Topiramate (Topamax): introduction of new safety measures, including a Pregnancy Prevention Programme - GOV.UK (www.gov.uk).

## Next steps

The Scottish Government's Anti-Seizure Medicines Task and Finish Group (a sub-group of the Teratogenic Medicines Advisory Group, TMAG) issued an assurance checklist for the prescribing of topiramate to patients who may be able to get pregnant, to all Health Boards in Scotland. The checklist aims to support Health Boards in Scotland with internal assurance processes. It follows a similar checklist on valproate.

In addition, my officials will continue to engage with the MHRA on all medicine safety issues.

I hope that this update to the Committee is helpful.

Yours sincerely,

**Jenni Minto MSP**



Taigh Naomh Anndrais, Rathad Regent, Dùn Èideann EH1 3DG
St Andrew's House, Regent Road, Edinburgh EH1 3DG
www.gov.scot



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