East Lancashire Health Economy Medicines Management Board
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# MHRA Drug Safety Update

December 2022

MHRA Regulating Medicines and Medical Devices

**Valproate: reminder of current Pregnancy Prevention Programme requirements; information on new safety measures to be introduced in the coming months**

In view of data showing ongoing exposure to valproate in pregnancy, the MHRA is reminding healthcare professionals of the risks in pregnancy and the current Pregnancy Prevention Programme requirements. The MHRA has also provided information about the potential risks of valproate in other patients following a review of the latest safety data. Following advice from the Commission on Human Medicines (CHM), new safety measures for valproate-containing medicines are to be put in place in the coming months.

**Current safety measures for valproate due to risks with pregnancy exposure**

Due to the serious harms to an unborn baby associated with use of valproate in pregnancy, the existing advice is that valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated. As a further strengthening of this position in April 2018, the MHRA introduced the Valproate Pregnancy Prevention Programme (PPP) as a requirement of any valproate use in patients of childbearing potential. The MHRA is continuing to closely monitor the impact of these requirements.

**Safety review of data relating to valproate**

In 2022, the Commission on Human Medicines (CHM) considered a review of safety data relating to valproate. This review included prescribing data showing continued use of valproate in female patients and also some use during pregnancy, as well as evolving information about potential risks in male patients. The latest report of the registry, published September 2022, noted that 17 female patients prescribed valproate in a month in which they were pregnant were identified as new additions to the registry between October 2021 and March 2022.

The review also considered data for other potential risks, including that, as indicated in the current product information, valproate may impair male fertility, and there is some evidence that this is reversible upon discontinuation. In addition, data were considered from studies in juvenile rats and adult rats and dogs reporting adverse effects to the male reproductive system in animals receiving valproate, as well as non-clinical studies on the potential for epigenetic effects of valproate and transgenerational risks. There are currently limited data available on these risks in humans and further studies are planned. There is also an ongoing retrospective study on the outcomes of babies exposed to valproate via paternal use.

**CHM advice and recommended new measures**

On the basis of the evidence, the CHM has recommended a number of regulatory actions to further strengthen safety measures for valproate. These measures will be introduced over the coming months according to patient priorities so they can be introduced safely. Advice on the timing of introduction will be provided once the CHM's implementation group has finalised plans and after full engagement with stakeholders. No action is needed at present except for women of childbearing potential not on the Pregnancy Prevention Programme.

The CHM recommends that no patients (male or female) under the age of 55 years should be initiated on valproate unless 2 specialists independently consider and document that there is no other effective or tolerated treatment. For patients under 55 years currently receiving valproate, 2 specialists should independently consider and document that there is no other effective or tolerated treatment or the risks do not apply. The CHM has advised that these measures should apply to people under the age of 55 because this is the age group most likely to be affected by the risks of valproate when taken during pregnancy and the possible risk of impaired fertility in males. Other measures recommended by CHM included further warnings in the product information, improved educational materials, and better monitoring of healthcare professionals' compliance with the new measures.

Full adherence to the Valproate Pregnancy Prevention Programme must continue. This includes the need for annual review and a signed Acknowledgement of Risk Form. All patients who think they are pregnant while on valproate should be advised to talk to a specialist urgently. Patients currently taking valproate must be advised not to stop taking it unless they are advised by a specialist to do so.