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13 Dec 2022

Dear Healthcare Professionals,

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

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that, in view of data showing ongoing exposure to valproate in pregnancy, MHRA reminds healthcare professionals of the risks in pregnancy and the current Pregnancy Prevention Programme requirements, and provides 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.

Valproate (as sodium valproate or valproic acid) has a high teratogenic potential. Exposure of an unborn child to valproate in utero is associated with a high risk of congenital malformations (11%) and neurodevelopmental disorders (30 - 40%), which may lead to permanent disability. The available evidence does not support a specific at-risk gestational period and the possibility of a risk of valproate throughout pregnancy cannot be excluded. 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 Apr 2018, MHRA introduced the Valproate Pregnancy Prevention Programme as a requirement of any valproate use in patients of childbearing potential.

In 2022, the 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 CHM also considered the views of patients and other stakeholders on the current use of valproate and on how the risks of valproate are currently managed.

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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.

Advice for healthcare professionals:

- Continue to follow the existing strict precautions, including that valproate should not be prescribed to female children or women of childbearing potential unless 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.
- Following a new safety review conducted in light of concerns that the current regulatory requirements for safe use are not being consistently followed, the CHM has advised that there should be greater scrutiny of the way valproate is prescribed and that further risk minimisation measures are required - in particular that 2 specialists should independently consider and document that there is no other effective or tolerated treatment for patients aged under 55 years.
- Consider all other suitable therapeutic options before newly prescribing valproate in patients younger than 55 years.
- These new measures will be implemented over the coming months.
- Patients currently taking valproate must be advised not to stop taking it unless they are advised by a specialist to do so.

Please refer to the following website in MHRA for details:

<https://www.gov.uk/drug-safety-update/valproate-reminder-of-current-pregnancy-prevention-programme-requirements-information-on-new-safety-measures-to-be-introduced-in-the-coming-months>

In Hong Kong, there are 10 registered pharmaceutical products containing valproate. All products are prescription-only medicines. So far, the Department of Health (DH) has received 14 cases of adverse drug reaction related to valproate, but these cases were not related to the risks in pregnancy or impaired fertility in males.

Related news on the risks in pregnancy associated with the use of valproate was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 2 Jul 2011, with the latest update posted on 24 Jun 2019. Letters to inform local healthcare professionals were issued by the DH on 4 Jul 2011, 7 May 2013, 13 Oct 2014 and 12 Feb 2018.

The Registration Committee of the Pharmacy and Poisons Board discussed the matter related to the risks in pregnancy associated with the use of valproate in Sep 2011, Dec 2014, Dec 2018 and Jun 2019. Currently, the package insert or sales pack label of locally registered valproate-containing products should include safety information on the risk of malformations and impaired cognitive development in children exposed to valproate during pregnancy, and contraindications, e.g. in women of childbearing potential unless pregnancy preventive measures have been implemented, etc. The certificate holders of locally registered valproate-containing products are also required to implement risk minimisation measures, e.g. patient information leaflet should be provided, etc.

In light of the above MHRA's announcement, the matter will be further discussed by the Registration Committee of the Pharmacy and Poisons Board.

Please note that this letter serves as a means for the DH to communicate important new safety information about registered pharmaceutical products with healthcare professionals in Hong Kong and is not intended to serve as guidelines or to replace professional clinical judgement. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Adverse Drug Reaction Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: [adr@dh.gov.hk](mailto:adr@dh.gov.hk)). For details, please refer to the website at Drug Office under "ADR Reporting": <http://www.drugoffice.gov.hk/adr.html>. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,



PP (Terence MAN)  
for Assistant Director (Drug)