Medicines & Healthcare products
Regulatory Agency

MHRA

Ms Joanna Wood
Review Team
Independent Medicines and Medical
Devices Safety Review
King's College,
London
SE1 1UL

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Medicines and Healthcare products Regulatory Agency

10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

+44 (0) 20 3080 6000

gov.uk/mhra

Dear Ms Wood

Thank you for your letter of 12 April giving the opportunity to respond to points made in the transcript of Dr Jim Morrow's oral evidence to the Review.

To provide some background, Dr Morrow, was invited by MHRA in view of his knowledge and experience as Founder and Principal Investigator of the UK Epilepsy and Pregnancy Register, to participate in two Registry Workshop meetings (on 19th November 2018 and 13 February 2019) to provide advice on establishing the UK Valproate Registry.

Dr Morrow kindly agreed and also asked if he could join the wider Valproate Stakeholder Network (VSN) meetings taking place just prior to the Valproate Registry workshop meetings on each of those dates. Dr Morrow was therefore included in some of the discussions of the VSN which focussed on the progress with implementation of the Valproate Pregnancy Prevention Programme. Dr Morrow took the opportunity to raise the teratogenic effects of topiramate in the VSN meetings.

The teratogenic effects of topiramate are well established and are reflected in authorised product information. The Summary of Product Characteristics (SmPC) for topiramate states a prevalence of major congenital malformations (MCM) of 4.3% (based on the North American Antiepileptic Drug pregnancy registry data). There is also a higher prevalence of low birth weight and of being small for gestational age with topiramate versus the reference group from this dataset.

This is consistent with data from the UK and Ireland Epilepsy and Pregnancy Register[1] which has a rate of MCM for topiramate monotherapy of 4.72 (95% CI 1.97-10.14). The rate of MCM with topiramate in polytherapy was 8.19% although the increase seems to be mainly due to polytherapy with valproate.

The regulatory position is that topiramate is licensed for use in migraine prophylaxis and is contraindicated in pregnancy and in women of childbearing potential unless pregnancy is excluded before treatment and a highly effective method of contraception is used during treatment.

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1 https://www.researchgate.net/publication/317069291_What_happened_to_Topiramate_An_update_from_the_UK_and_Ireland_Epilepsy_and_Pregnancy_Register

For the epilepsy indication, the SmPC states that *'It is recommended to consider alternative therapeutic options in women of child bearing potential. If topiramate is used in women of childbearing potential, it is recommended that highly effective contraception be used (see section 4.5), and that the woman is fully informed of the known risks of uncontrolled epilepsy to the pregnancy and the potential risks of the medicinal product to the fetus. If a woman plans a pregnancy, a preconceptional visit is recommended in order to reassess the treatment, and to consider other therapeutic options. In case of administration during the first trimester, careful prenatal monitoring should be performed.'*

Given the known use of valproate in migraine outside its licensed indications in the UK, the patient representatives from relevant organisations representing migraine sufferers have been fully involved and have contributed to the Valproate Stakeholder Network.

We continually monitor the safety of all medicines in pregnancy and will be consulting the Commission on Human Medicines on an overall review of the available evidence on the risks of all antiepileptics in pregnancy in the coming weeks.

Please let me know if you require further clarification.

Yours sincerely

June M. Raine

Dr June Raine
Director – Vigilance and Risk Management of Medicines

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