Health Canada
Health Products and Food Branch

Santé Canada
Direction générale des produits de santé et des aliments

Marketed Health Products Directorate
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Date: September 25, 2023

DSTS Control #: 278408

Re: topiramate use in women of childbearing potential

Topiramate is already known to cause serious birth defects when used during pregnancy; safety information is already included in the Canadian label. However, further to recently available data and international regulatory activities, we would like to request feedback from the **Canadian Neurological Society (CNS)** on risk minimization measures (RMMs) for topiramate use in women of childbearing potential to mitigate the potential risk of fetal harm.

Janssen Inc. (the market authorization holder [MAH] for TOPAMAX®) has updated their Canadian Product Monograph[1] (CPM) in June 2023 to inform of new data suggesting an increased risk of neurodevelopmental disorders (NDD) associated with topiramate use in utero, based on a large multinational cohort study.[2] This new safety information is now captured in the Warnings and Precautions section of the CPM. Subsequently, 2 additional studies[3, 4] have been published since the initial cohort study.

Overall, 2 of the 3 studies suggest that children born to mothers with epilepsy and who were exposed to topiramate in utero may have a two- to three-fold higher risk of neurodevelopmental disorders, in particular autism spectrum disorder, intellectual disability or attention deficit hyperactivity disorder, compared with children born to mothers with epilepsy not

1 TOPAMAX product monograph. https://pdf.hres.ca/dpd_pm/00071444.PDF Date of Revision: June 30, 2023
2 Bjork MH, Zoega H, Leinonen MK, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. JAMA Neurology. 2022;79(7):672–681. doi:10.1001/jamaneurol.2022.1269
3 Dreier JW, Bjork MH, Alvestad S, et al. Prenatal exposure to antiseizure medication and incidence of childhood- and adolescence-onset psychiatric disorders. JAMA Neurology. 2023;80(6):568-577. doi:10.1001/jammaneurol.2023.0674
4 Hernandez-Diaz S, Straub L, Bateman B, et al. Topiramate during pregnancy and the risk of neurodevelopmental disorders in children. In Pharmacoepidemiology and Drug Safety 2022 September (Vol 31,pp:11-11) Wiley. Abstract #47. Accessed at https://doi.org/10.1002/pds.5518

taking antiepileptic medication. The 3rd study did not show an increased risk of these outcomes in children born to mothers exposed to topiramate in pregnancy, compared with children born to women with epilepsy not taking antiepileptic medication.

Based on these data, the Europeans Medicines Agency (EMA) is planning to put in place new measures to avoid exposure of children to topiramate in the womb.[5] As such, Health Canada is currently conducting a review to determine whether there is a need to add new measures in Canada [e.g. educational materials, expanding the contraindication to patients with epilepsy, a pregnancy prevention program (PPP)] to enforce the messages included in the CPM and to ensure that the risk of congenital malformations/NDD is appropriately managed.

Examples of elements in a PPP, include but are not limited to the following:

- Assessing each female patient's potential for becoming pregnant
- Counselling about alternate therapeutic options, risks associated with topiramate use during pregnancy, and need for highly effective contraception for the duration of treatment
- A one time or periodic risk acknowledgement where the prescriber and patient review and confirm that patient counselling was completed and the risk understood
- Regular review (e.g. annually) of treatment by a specialist
- Provision of a patient guide and/or wallet card to each patient
- Health care provider education

Health Canada is seeking your clinical input on the following:

1. Do you consider that labelling alone is sufficient to manage the risk of fetal malformation/NDD for topiramate, or is there a need for additional RMMs to mitigate the risk.
    a. If yes, please provide your views as to the type of measures recommended (e.g. educational materials).
2. Whether a PPP is needed to enforce the instructions for use in the CPM and ensure that the risk of fetal malformations/NDD associated with the use of topiramate during pregnancy are properly mitigated.
    a. If yes, please provide your recommended elements of the PPP.
3. Please provide comments on the feasibility and possible impact of the recommended measures on clinical practice, clinical workflow and patient impact as deemed applicable.
4. Please provide your views on the potential addition of a contraindication regarding the use of topiramate for the management of epilepsy unless there is no suitable alternative.
5. Please provide any additional comments you have on this issue.

5 https://www.ema.europa.eu/en/documents/referral/topiramate-article-31-referral-prac-recommends-new-measures-avoid-topiramate-exposure-pregnancy_en.pdf

Questions concerning this request should be directed to Papa Diogoye Sene, Regulatory Project Manager, Regulatory Project Management Office, MHPD, by email at mpb.rpm-gpr.bppc@hc-sc.gc.ca.

A response by October 25, 2023 would be very helpful. Please let us know if more time is required. Your assistance and advice in this matter are greatly appreciated. Please provide a response by email to: mpb.rpm-gpr.bppc@hc-sc.gc.ca.

Sincerely,

Rania Mouchantaf, PhD
Acting Director
Marketed Pharmaceuticals Bureau
Marketed Health Products Directorate

This document has been signed electronically using the Health Canada docuBridge system. /
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