HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

## Topiramate: Introduction of a pregnancy prevention programme in the EU

The European Medicines Agency's (EMA) announced on the 1st of September that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended the introduction of a pregnancy prevention programme[1] for topiramate in the EU. Topiramate is indicated in various forms of epilepsy and for the prophylaxis of migraine[2].

The PRAC recommendation follows a review of available data, including that from recent observational studies. Two of these studies, both of which used largely the same datasets, 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 (NDD), in particular autism spectrum disorders, intellectual disability or attention deficit hyperactivity disorder (ADHD), compared with children born to mothers with epilepsy not taking antiepileptic medication[3,4]. A third study, using a different dataset, did not show an increased risk of these outcomes[5]. The review also confirmed the known risk that topiramate can cause major congenital malformations (MCM) and foetal growth restriction (small for gestational age [birth weight below the 10th percentile corrected for their gestational age, stratified by sex] and low birth weight [<2,500 grams]) when used during pregnancy.

The PRAC has recommended the strengthening of existing restrictions and enhancement of risk minimisation measures across both epilepsy and migraine prophylaxis indications, which together will form a pregnancy prevention programme, based on the review of available data on the risk of NDD, and taking into consideration the existing knowledge of an increased risk of MCM and effects on foetal growth.

It is anticipated that in the coming months, the marketing authorisation holder (MAH) for topiramate in Ireland will apply to the HPRA to change the terms of their marketing authorisations (licenses) in accordance with the PRAC recommendations. Following HPRA approval, a direct healthcare professional communication and educational materials will be distributed.

### Pregnancy prevention programme (PPP)

The following is a summary of the measures which form part of the recommended PPP.

Contraindications for use:

Topiramate for migraine prophylaxis is **contraindicated:**

- in pregnancy
- in women of childbearing potential not using highly effective contraception.

Topiramate for epilepsy is **contraindicated:**

- in pregnancy, unless there is no suitable alternative treatment,
- in women of childbearing potential not using highly effective contraception. The only exception is a woman for whom there is no suitable alternative but who plans a pregnancy and who is fully informed about the risks of taking topiramate during pregnancy.

In female children and women of childbearing potential:

- Treatment with topiramate should be initiated and supervised by a physician experienced in the management of epilepsy or migraine. Alternative therapeutic options should be considered.
- The need for topiramate treatment in these populations should be reassessed at least annually.

In women of childbearing potential

- Patients must be fully informed and understand the potential risks related to the use of topiramate during pregnancy. This includes the need for a specialist consultation if the woman is planning a pregnancy and for prompt contact with a specialist if she becomes pregnant or thinks she may be pregnant.
- Pregnancy testing should be performed before initiating treatment.
- At least one highly effective method of contraception or two complementary forms of contraception including a barrier method should be used during treatment and for at least 4 weeks after stopping treatment. Women using systemic hormonal contraceptives should be advised to also use a barrier method due to interactions.
- If a woman is planning to become pregnant, efforts should be made to switch to an appropriate alternative epilepsy or migraine treatment before contraception is discontinued. For the treatment of epilepsy, the woman must also be informed about the risks of uncontrolled epilepsy to the pregnancy.
- If a woman being treated with topiramate for migraine prophylaxis becomes pregnant, treatment should be stopped immediately. The woman should be referred to a specialist for careful antenatal monitoring and counselling.
- If a woman being treated with topiramate for epilepsy becomes pregnant, she should promptly be referred to specialists to reassess topiramate treatment and consider alternative treatment options, as well as for careful antenatal monitoring and counselling.

In female children:

- Prescribers must ensure that parent(s)/caregiver(s) of female children using topiramate understand the need to contact a specialist once the child experiences menarche.
- At that time, the patient and parent(s)/caregiver(s) should be provided with comprehensive information about the risks due to topiramate exposure in utero, and the need for using highly effective contraception.

## Educational materials and product information/packaging updates

Following adoption at EU level and HPRA approval, further communications will be issued on the pregnancy prevention programme including guides for healthcare professionals and patients, a risk awareness form to be signed on treatment initiation and annually, and a patient card to be provided when the medicine is dispensed. A text warning and a pictogram on the teratogenic risk will be introduced on new product packaging. Product information* will be updated to include details of the pregnancy prevention programme.

## References

1.PRAC PPP Recommendations: https://www.ema.europa.eu/en/news/prac-recommends-new-measures-avoid-topiramate-exposure-pregnancy
2.Topamax product information accessible from https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Topamax
3.Bjørk M, Zoega H, Leinonen MK, et al. Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. JAMA Neurol. 2022 Jul 1;79(7):672-681. doi: 10.1001/jamaneurol.2022.1269.
4.Dreier JW, Bjørk M, Alvestad S, et al. Prenatal Exposure to Antiseizure Medication and Incidence of Childhood- and Adolescence-Onset Psychiatric Disorders. JAMA Neurol. 2023 Jun 1;80(6):568-577. doi: 10.1001/jamaneurol.2023.0674.
5.Hernandez-Diaz S, Straub L, Bateman B, et al. Topiramate During Pregnancy and the Risk of Neurodevelopmental Disorders in Children. In: ABSTRACTS of ICPE 2022, the 38th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE), Copenhagen, Denmark, 26–28 August, 2022. Pharmacoepidemiol Drug Saf, 2022; 31 Suppl 2:3-678, abstract 47.

*The approved product information is comprised of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available from www.hpra.ie and www.ema.europa.eu.