EMA review of topiramate

Potential risk of neurodevelopmental disorders

You may have read by now that the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) has started a review of topiramate and the risk of neurodevelopmental disorders in children who were exposed during pregnancy. Topiramate is available in Ireland as Topamax tablets, and Topamax sprinkle capsules.

Topamax is indicated in the following conditions:

- Monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures
- Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures, with or without secondary generalisation or primary generalised tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome
- In adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Not intended for acute treatment

Use of topiramate in pregnant women is already known to increase the risk of birth defects. Women with epilepsy who are being treated with topiramate for their seizures are advised to avoid becoming pregnant, and to consult their doctor for advice if they wish to become pregnant.

Topiramate is contra-indicated in migraine prophylaxis in pregnant women and in women of childbearing potential who are not using highly effective birth control methods.

The current review has been initiated following the publication of a study investigating the risk of neurodevelopmental disorders, including autism spectrum disorder and intellectual disability in association with parental exposure to various anti-epileptic drugs (AEDs). The study showed that prenatal exposure to topiramate was associated with increased risk of neurodevelopmental disorders. The EMA is therefore now undertaking an in-depth evaluation of these potential risks.

Current warnings and restrictions

The SPC for Topamax currently includes the following warnings regarding the use of topiramate in women of childbearing potential and in pregnancy.

Women of childbearing potential

Topiramate may cause foetal harm and foetal growth restriction when administered to a pregnant woman. The North American Antiepileptic Drug pregnancy registry data for topiramate monotherapy showed an approximate 3 fold higher prevalence of major congenital malformations (4.3%), compared with a reference group (1.4%). Data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of AEDs in combination therapy.

Before the initiation of treatment with topiramate in a woman of childbearing potential, pregnancy testing should be performed, and a highly effective contraceptive method advised. The patient should be fully informed of the risks related to the use of topiramate during pregnancy.

Pregnancy

Specialist advice should be given to women who are of childbearing potential. The need for treatment with AEDs should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.

Clinical data from pregnancy registries indicate that infants exposed to topiramate monotherapy have:

- An increased risk of congenital malformations (particularly cleft lip/palate, hypospadias, and anomalies involving various body systems) following exposure during the first trimester. The risk has been reported to be dose dependent.
- A higher prevalence of low birth weight (<2500 grams) compared with a reference group
- An increased prevalence of being small for gestational age

HPRA Drug Safety Newsletter

In the August 2022 Newsletter the HPRA sought to remind all healthcare professionals of the current warnings and restrictions regarding use in pregnancy and in women of childbearing potential.

Pending the outcome of the EMA study, healthcare professionals should also take into account the potential risk of neurodevelopmental disorders when discussing topiramate therapy with women of childbearing potential and in case of pregnancy.

Further reading

- HPRA Drug Safety Newsletter 108th Edition, August 2022 'Topiramate – commencement of EU review regarding potential risk of neurodevelopmental disorders in children exposed in utero *https://www.hpra.ie/docs/default-source/publications-forms/newsletters/hpra-drug-safety-newsletter-edition-108.pdf?sfvrsn=5*
- HPRA Drug Safety Newsletter 106th Edition, February 2022 'Review of latest evidence on risks associated with in-utero exposure to phenytoin, phenobarbital, carbamazepine, pregabalin and valproate *https://www.hpra.ie/docs/default-source/publications-forms/newsletters/hpra-drug-safety-newsletter-edition-106.pdf?sfvrsn=5*
- EMA Meeting highlights from PRAC 29 August – 1 September 2022 *https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-29-august-1-september-2022*