HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Topiramate: Introduction of a pregnancy prevention programme and new restrictions on use

Key Message

- Topiramate can cause major congenital malformations and foetal growth restriction when used during pregnancy. Recent data also suggest a possibly increased risk of neurodevelopmental disorders (NDD) including autism spectrum disorders, intellectual disability, and attention deficit hyperactivity disorder (ADHD) following topiramate use during pregnancy.
- New contraindications apply for the treatment of epilepsy:
  - 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.
- Topiramate for prophylaxis of migraine is already contraindicated in pregnancy and in women of childbearing potential not using highly effective contraception.
- Treatment of women of childbearing potential should be initiated and supervised by a physician experienced in the management of epilepsy or migraine. The need for treatment should be reassessed at least annually.
- Due to a potential interaction, women using systemic hormonal contraceptives should be advised to also use a barrier method.
- For women of childbearing potential currently using topiramate, the treatment should be re-evaluated to ensure that the measures of the pregnancy prevention programme (key elements described below) are followed.

Topiramate is indicated in children, adolescents, and adults in various forms of epilepsy as mono or adjunctive therapy, and in adults for prophylaxis of migraine after careful evaluation of possible alternative treatment options*.

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has recommended new measures to avoid exposure to topiramate during pregnancy in the form of a pregnancy prevention programme (PPP) and further restrictions on use. This follows a review of data suggesting a possible increased risk of neurodevelopmental disorders (NDD), including autism spectrum disorders, intellectual disability, and attention deficit hyperactivity disorder (ADHD) following topiramate use during pregnancy.

As described in Edition 108 of the HPRA Drug Safety Newsletter, the review by the PRAC[1] was initiated following the recent publication of data from observational studies. Over the course of the review, the PRAC considered the available observational study data on NDD, as follows:

- Two observational population-based registry studies[2,3] undertaken in largely the same dataset from Nordic countries. The results of these studies suggest there may be a 2- to 3-fold higher prevalence of autism spectrum disorders, intellectual disability, or attention deficit hyperactivity disorder (ADHD) in almost 300 children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to an anti-epileptic drug (AED).

- A third observational cohort study[4] from the U.S.A. did not suggest an increased cumulative incidence of these outcomes by 8 years of age in approximately 1000 children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to an AED.

The PRAC review has also confirmed the well-known increased risk of major congenital malformation (MCM) and foetal growth restriction (low birth weight and small for gestational age) associated with topiramate use during pregnancy:

- Infants exposed to topiramate monotherapy in utero have an approximately 3-fold increased risk of major congenital malformations including cleft lip/palate, hypospadias and anomalies involving various body systems compared with a reference group not exposed to antiepileptic drugs. Absolute risks of major congenital malformations following topiramate exposure have been reported in the range of 4.3% (1.4% in the reference group) to 9.5% (3% in the reference group)[5].

- Data from pregnancy registries indicated a higher prevalence of low birth weight (< 2,500 grams) and of being small for gestational age (SGA; defined as birth weight below the 10th percentile corrected for their gestational age, stratified by sex) for topiramate monotherapy. In the North American Antiepileptic Drug Pregnancy Registry, the risk of SGA in children of women receiving topiramate was 18%, compared with 5% in children of women without epilepsy not receiving an AED[6].

Based on review of observational data suggesting a possibly increased risk of NDD, in addition to the confirmation of the known risks of MCM and foetal growth restriction, the PRAC recommended further restrictions on use of topiramate and the introduction of a pregnancy prevention programme in the EU, key elements of which are described below.

For women of childbearing potential currently using topiramate, the treatment should be re-evaluated to ensure that the measures of the pregnancy prevention programme (key elements described below) are followed.

Key elements of the pregnancy prevention programme

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 (use in this indication for women of childbearing potential only).
- 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:
- 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.
- Pregnancy testing should be performed before initiating treatment.
- The patient 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 pregnancy and for prompt contact with a specialist doctor if she becomes pregnant or thinks she may be pregnant.
- At least one highly effective method of contraception (such as an intrauterine device) or two complementary forms of contraception including a barrier method should be used during treatment and for at least 4 weeks after stopping treatment. Due to a potential interaction, women using systemic hormonal contraceptives should be advised to also use a barrier method.
- If a woman is planning to become pregnant, efforts should be made to switch to 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 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.
- If a woman being treated with topiramate as migraine prophylaxis becomes pregnant, treatment should be stopped immediately. The woman should be referred to a specialist for careful antenatal monitoring and counselling.

In female children (for epilepsy only):
- 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

Educational materials will be developed and circulated to assist healthcare professionals and patients in following the pregnancy prevention programme and in avoiding exposure to topiramate during pregnancy.

These will include:
- A guide for HCPs involved in the care of female children and women of childbearing potential
- A risk awareness form, which must be used and signed at the time of treatment initiation and during each annual review of topiramate treatment by the treating physician
- A patient guide which should be provided to all female children or their parent(s)/caregiver(s) and women of childbearing potential
- A patient card, which should be provided each time the medicine is dispensed. The card will be either included inside the package or attached to the outer packaging.

Educational materials will be made available on the HPRA website (www.hpra.ie) and will be circulated in hard copy by the marketing authorisation holder for topiramate, following approval by the HPRA.

A textual warning and a pictogram on the teratogenic risk will be introduced as an addition to the outer package of all topiramate-containing medicinal products.

A Direct Healthcare Professional Communication (DHPC)[7] to inform healthcare professionals of the outcome of the review has been distributed in Ireland.

*Indicated as 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, and as 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. Topiramate is indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Further details on topiramate containing medicines are available at www.hpra.ie.

References

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