Janssen Sciences Ireland UC

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PLEASE READ

IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

1st November 2023

Topiramate: New restrictions to prevent exposure during pregnancy

Dear Healthcare Professional,

This letter is sent in agreement with the European Medicines Agency (EMA) and with the Health Products Regulatory Authority (HPRA) to inform you of the implementation of a **pregnancy prevention programme for topiramate-containing medicinal products**.

Summary

- **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 female children (in the case of epilepsy) and women of childbearing potential (for epilepsy and migraine) 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.**

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Background on the safety concern

Topiramate is 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.
- 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.
- Prophylaxis of migraine headache in adults after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment.

Data from two observational population-based registry studies (1, 2) undertaken in largely the same dataset from the Nordic countries suggest that there may be a 2- 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 (3) 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.

It is already well known that topiramate can cause major congenital malformations and foetal growth restriction when used 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) (4).
- 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 (5).

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

Key elements of the pregnancy prevention programme

<u>In female children and women of childbearing potential:</u>

- 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.

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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 a pregnancy and for prompt contact with a specialist 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. 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 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 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 material

In order to assist healthcare professionals and patients in avoiding exposure to topiramate during pregnancy and to provide information about the risks of taking topiramate during pregnancy, educational materials will be put in place including:

- a guide for healthcare professionals involved in the care of female children and women of childbearing potential using topiramate including 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,

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- a patient guide which should be provided to all female children or their parent(s)/caregiver(s) and women of childbearing potential using topiramate,
- a patient card (included in or attached to the outer package), so that it will be provided to the patient each time the medicine is dispensed.

A textual warning and a pictogram on the teratogenic risk will be added to the outer package of all topiramate containing medicinal products.

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with these products in accordance with the national spontaneous reporting system via the HPRA Pharmacovigilance, website www.hpra.ie.

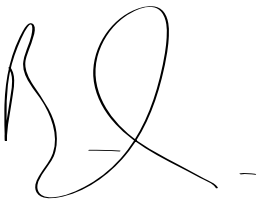
When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset dates, treatment dates, product brand name and batch numbers.

Suspected adverse reactions should also be reported to Janssen on tel.: 0044(0)1494 567447, fax: +44(0)1494 567799 or by e-mail at dsafety@its.jnj.com.

Company Contact Point

If you have further questions, please do not hesitate to contact the Janssen Medical Information department on tel.: 1 800 709122 or email: medinfo@its.jnj.com

Yours faithfully,



Dr Bríd Seoighe
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