22-Aug 2025

TOPIRAMATE-Actavis® (Topiramate): New Restrictions to Prevent Exposure During Pregnancy

Dear Healthcare Professional,

In agreement with Medsafe in New Zealand, Teva Pharma (New Zealand) Ltd would like to inform you of the implementation of pregnancy prevention measures for topiramate-containing medicinal products.

Summary of Safety Measures:

- Topiramate can cause major congenital malformations and fetal growth restriction when used during pregnancy.
- Recent data suggests an increased risk of neurodevelopmental disorders (NDD), including:
    - Autism spectrum disorders (ASD)
    - Intellectual disability
    - Attention deficit hyperactivity disorder (ADHD)
- For migraine prophylaxis, topiramate is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraception
- The necessity of treatment should be reassessed annually.
- Women using systemic hormonal contraceptives should also use a barrier method.
- At the next appointment for women of childbearing potential currently using topiramate, the treatment should be re-evaluated to confirm that pregnancy prevention measures are adhered to.
- Physicians must counsel women of childbearing potential on risks of topiramate use and epilepsy during pregnancy. If pregnancy occurs during treatment, conduct a thorough assessment, inform the patient of the potential fetal hazard, and provide advice to the patient on the risks versus benefits of continuing treatment.

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Please find below some background information on the safety concern as follows:

Background on the safety concern

Indications:

A) Epilepsy

Topiramate-Actavis is indicated in adults and children 2 years and older:

- As monotherapy in patients with newly diagnosed epilepsy
- For conversion to monotherapy in patients with epilepsy
- As add-on therapy for:
    - Partial onset seizures
    - Generalised tonic-clonic seizures
    - Seizures associated with Lennox-Gastaut syndrome

B) Migraine

Topiramate-Actavis is indicated in adults for the prophylaxis of migraine headache. Its effectiveness for acute migraine treatment has not been studied.

Supporting Study Data

Two Nordic registry studies suggest a 2–3-fold increased prevalence of ASD, intellectual disability, or ADHD in children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to an antiepileptic drug.'.

A third observational cohort study from the U.S.A. did not suggest an increased cumulative incidence of these outcomes by 8 years of age in 1030 children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to topiramate, after adjustment for indication and other confounders.

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It is already well known that topiramate can cause major congenital malformations and fetal growth restriction when used during pregnancy. 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 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 not taking AEDs (1.4%). In addition, 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. The risk has been reported to be dose dependent; effects were observed in all doses.
- A higher prevalence of low birth weight (<2500 grams) compared with a reference group.
- An increased prevalence of being small for gestational age (SGA; defined as birth weight below the 10th percentile corrected for their gestational age, stratified by sex). The long-term consequences of the SGA findings could not be determined.

At the next appointment for women of childbearing potential currently using topiramate, the treatment should be re-evaluated to confirm that the pregnancy prevention measures are adhered to.

Key Elements of the Pregnancy Prevention Measures

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, respectively.
- 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 and in women of childbearing potential not using highly effective contraception.
- 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:

- 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

To assist healthcare professionals (HCPs) 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 HCPs involved in the care of female children and women of childbearing potential using topiramate including a risk awareness form, which could 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 using topiramate.

An electronic copy of the HCP guide and Patient guide is available on the Teva Pharmaceuticals website:

https://www.tevapharm.co.nz/hcp-portal/topiramate

Patients can access an electronic version of the patient guide here:

https://www.tevapharm.co.nz/patient-portals/topiramate

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

Please refer to the Topiramate-Actavis Data Sheet for complete prescribing information, available from website:
https://www.medsafe.govt.nz/profs/datasheet/t/topiramateactavistab.pdf

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Adverse Event Reporting

Please report any suspected adverse reactions/events associated with the use of Topiramate-Actavis to Medsafe/Centre for Adverse Reactions Monitoring at https://pophealth.my.site.com/carmreportnz/s/

and to below company contact point:

Teva drug safety reporting: Safety.Australia@tevapharm.com or
N.Z. Phone: 0800 800 097 (Option 1)

For further information, please contact Teva Pharma New Zealand Ltd via email:
MedInfo.ANZ@tevapharm.com

Yours faithfully,

Dr. H.H. Teh

Medical Affairs Director

Teva Pharma Australia Pty. Ltd.

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