

IMPORTANT MEDICINE SAFETY INFORMATION:**TOPIRAMATE – RISK OF NEURODEVELOPMENT DISORDERS ASSOCIATED WITH USE IN PREGNANCY****21 April 2026**

Dear Healthcare Professional

Janssen Pharmaceutica (Pty) Ltd, in collaboration with the South African Health Products Regulatory Authority (SAHPRA) would like to inform you of the risk of neurodevelopment disorders (NDDs) associated with topiramate use in pregnancy.

A Pregnancy Prevention Programme for topiramate-containing medicinal products as per below should be implemented and the professional information and patient information leaflet will be updated accordingly.

Summary

- Topiramate can cause major congenital malformations and foetal growth restriction when used during pregnancy. Recent data suggest a possibly increased risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD), intellectual disability and attention deficit hyperactivity disorder (ADHD) following topiramate use during pregnancy.
- Topiramate use is contraindicated during pregnancy, unless there is no suitable treatment alternative.
- Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
- Topiramate must be discontinued if the patient becomes pregnant or is planning to conceive, unless there is no suitable treatment alternative.
- The need for treatment with topiramate should be reassessed at least annually.
- Women of childbearing potential should use highly effective contraception during treatment and for at least four (4) weeks after stopping topiramate treatment.
- Due to a potential interaction, women using systemic hormonal contraceptives should be advised to also use a barrier method.

- Healthcare professionals should ensure that women of childbearing potential treated with topiramate patients are fully informed of the known and potential risks related to the use of topiramate during pregnancy and the need for highly effective contraception.

Background on the safety concern

Topiramate is indicated to treat epilepsy as:

- monotherapy in patients with newly diagnosed epilepsy or for conversion to monotherapy in patients with epilepsy.
- adjunctive therapy for adults and children aged four (4) and above with partial onset seizures with or without secondarily or generalized; seizures associated with Lennox-Gastaut syndrome; and primary generalised tonic-clonic seizures¹.
- Adjunctive therapy in adults and children for the treatment of seizures associated with Lennox-Gastaut syndrome.

Data from two observational population-based registry studies^{2,3} undertaken in Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) suggest that there may be a 2- to 3-fold higher prevalence of ASD, ID or ADHD in almost 300 children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to antiseizure medication. A third observational cohort study⁴ from the United States, did not suggest an increased cumulative incidence of these outcomes by eight (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.

The use of topiramate in pregnancy is already known to increase the risk of major congenital malformations (3-fold increased risk compared with a reference group not taking antiseizure medication) and foetal growth restriction (low birth weight and small for gestational age).^{5,6}

Advice to healthcare professionals:

- Treatment with topiramate should be initiated and supervised by a physician experienced in the management of epilepsy.
- In treating and counselling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks and consider alternative therapeutic options, if this medication is used during pregnancy or if patient becomes pregnant while taking this medication, the patient should be apprised of the potential hazard to the foetus.
- The patient must be fully informed and understand the potential risks related to the use of topiramate during pregnancy. This includes the need to consult her doctor as soon as she is planning to conceive, and for prompt contact

with her doctor if she becomes pregnant or thinks she may be pregnant and is taking topiramate.

- 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 four (4) weeks after stopping treatment. Women using systemic hormonal contraceptives should be advised to also use a barrier method.
- A Pregnancy Prevention Programme should be implemented, as a risk minimisation measure, in women of childbearing potential consisting of the following elements:
 - pregnancy testing before initiating treatment with topiramate, and a highly effective contraceptive method advised;
 - a review of ongoing treatment at least annually by completion of a risk awareness form;
 - confirmation that appropriate measures have been taken, by going through the risk awareness from the beginning of treatment, at each annual review, and if the patient is planning to conceive or has become pregnant;
 - ensuring that the patient is fully informed and understands the risks related to the use of topiramate during pregnancy, and the measures needed to minimise the risk.
 - Switching to an appropriate alternative treatment before contraception is discontinued, if a woman is planning to become pregnant;
 - Prompt referral to a specialist for treatment reassessment if a woman being treated with topiramate for epilepsy becomes pregnant.

Advice for healthcare professionals to provide to patients

The patient must be fully informed and understand the risks related to the use of topiramate during pregnancy. This includes the need to consult a healthcare professional as soon as they are planning pregnancy, and for prompt contact with their healthcare provider if they become pregnant or think they may be pregnant and are taking topiramate. The patient should be informed that topiramate is contraindicated:

- in pregnancy unless there is no suitable alternative treatment;
- in patients of childbearing potential unless the conditions of Pregnancy Programme are fulfilled;

References:

1. Bjørk M, Zoega H, Leinonen MK, et al. Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. *JAMA Neurol*. Published online May 31, 2022. doi:10.1001/jamaneurol.2022.1269.
2. Dreier JW, Bjørk M, Alvestad S, et al. Prenatal Exposure to Antiseizure Medication and Incidence of Childhood- and Adolescence-Onset Psychiatric Disorders. *JAMA Neurol*. Published online April 17, 2023. doi: 10.1001/jamaneurol.2023.0674. Online ahead of print. PMID: 37067807.

3. Hernandez-Diaz S, Straub L, Bateman B, et al. Topiramate During Pregnancy and the Risk of Neurodevelopmental Disorders in Children. (2022), 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.
4. Cohen JM, Alvestad S, Cesta CE, et al. Comparative Safety of Antiseizure Medication Monotherapy for Major Malformations. Ann Neurol. 2023; 93(3):551-562.
5. Hernandez-Diaz S, McElrath TF, Pennell PB et al. Fetal Growth and Premature Delivery in Pregnant Women on Anti-epileptic Drugs. North American Antiepileptic Drug Pregnancy Registry. Ann Neurol. 2017 Sept;82 (3):457-465. doi:10.1002/ana.25031. PMI:28856694
6. Topalex® Professional Information, Janssen Pharmaceutica (Pty) Ltd May 2022

Call for reporting

- Healthcare professionals are urged to report any adverse drug reactions (ADRs) or product quality problems associated with the use of the listed products to the company below, or to SAHPRA via the e-Reporting link available on the SAHPRA website (www.sahpra.org.za).
- Alternatively, please complete the ADR reporting form accessible via the SAHPRA website at <https://www.sahpra.org.za/document/adverse-drug-reactions-and-qualityproblem-reportingform/> and email it to adr@sahpra.org.za. Additionally, reporting can be done via the Med Safety App. The App can be downloaded onto a smart mobile phone through Google Play or Apple App store. For more information on the Med Safety App, please visit the SAHPRA website.
- For more information on ADR reporting of the products listed below, please contact the SAHPRA Vigilance unit at pvqueries@sahpra.org.za or alternatively use the contact details indicated below.

Company contact point:

PRODUCTS	ACTIVE INGREDIENT	REGISTRATION NUMBER	CONTACT DETAILS Pharmacovigilance Unit
TOPAMAX® 25 MG; 50 MG; 100 MG; 200 MG/ TOPALEX® TABLETS 25 MG; 50 MG; 100 MG AND TOPAMAX® SPRINKLE CAPSULES 15 MG; 25 MG; 50 MG	Topiramate	30/2.5/0236-9 41/2.5/0622-4 32/2.5/0662-4	Tel: +2711 518 7100 Fax: +2786 687 8942 or +2711 518 7108 Email: AdverseEventZA@its.jnj.com

Yours sincerely,

Vanessa Snow

VANESSA SNOW – HEAD OF MEDICAL AFFAIRS