IMPORTANT MEDICINE SAFETY INFORMATION

TOPIRAMATE – RISK OF NEURODEVELOPMENTAL DISORDERS

12 March 2025

Dear Healthcare Professional,

In collaboration with the South African Health Products Regulatory Authority (SAHPRA), Ranbaxy Pharmaceuticals (Pty) Ltd South Africa, Zydus Healthcare SA (Pty) Ltd and, Trinity Pharma (Pty) Ltd wish to inform you about the risk of neurodevelopmental disorders in the children born to women exposed to topiramate during pregnancy.

The Professional Information (PI) and Patient Information Leaflet (PIL) will be updated accordingly.

Summary

- Topiramate can cause major congenital malformations and foetal growth restriction when used during pregnancy. Recent data also suggests that topiramate use during pregnancy may increase the risk of neurodevelopmental disorders (NDD) including autism spectrum disorders, intellectual disability and attention deficit hyperactivity disorder (ADHD).
- Topiramate is also contraindicated in women of childbearing potential with epilepsy not using highly effective contraception.
- Topiramate use is contraindicated during pregnancy, unless there is no suitable treatment alternative.
- Women of childbearing potential should use highly effective contraception during treatment and for at least 4 weeks after stopping topiramate treatment.
- Topiramate must be discontinued if the patient becomes pregnant or is planning to conceive, unless there is no suitable alternative.
- If a woman is planning a pregnancy or becomes pregnant, and requires treatment with topiramate, because there is no suitable treatment alternative, she must be fully informed about the risks associated with taking topiramate during pregnancy.
- Healthcare professionals should ensure that women of childbearing potential treated with topiramate are fully informed of the known and potential risks related to the use of topiramate during pregnancy and the need for highly effective contraception.
- An Annual Risk Awareness Form should be completed by the healthcare professional and a patient during treatment initiation and annually to ensure that both are aware of the risks of taking topiramate during pregnancy.

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.
- as adjunctive therapy for adults and children over 4 years of age who are inadequately controlled on conventional first line antiepileptic medicines for partial onset seizures with or without secondarily generalised seizures, seizures associated with Lennox-Gastaut syndrome and, primary generalized tonic clonic seizures.[1]

The use of topiramate in pregnant women is known to increase the risk of major congenital malformations (3-fold increased risk compared with a reference group not taking antiseizure medications) and foetal growth restriction (low birth weight and small for gestational age).[2]

A recent cohort study investigated the association between prenatal exposure to various antiseizure medications (ASM) including topiramate, and the risk of neurodevelopmental disorders, including autism spectrum disorder (ASD) and intellectual disability (ID). This study used data from several Nordic registries (Denmark, Finland, Iceland, Norway and Sweden), and included information from more than 24,000 children exposed to at least one ASM before birth. Of these children, 471 were exposed to topiramate alone, including 246 children born to mothers who had epilepsy. Prenatal exposure to topiramate was associated with an increased risk of ASD, ID and a combined outcome of any neurodevelopmental disorder. In children of mothers with epilepsy, the 8-year cumulative incidence of ASD was 4.3% with topiramate exposure, and 1.5% in those not exposed. The 8-year cumulative incidence of ID was 3.1% in topiramate exposed children, and 0.8%, in unexposed children. The adjusted hazard ratios for ASD and ID were 2.8 (95%CI, 1.4-5.7) and 3.5 (95%CI, 1.4-8.6), respectively.[2]

Advice to healthcare professionals[3]

- Topiramate treatment in women of childbearing potential should be initiated and supervised by a physician experienced in the management of epilepsy.

- Alternative therapeutic options should be considered and the need for treatment should be reassessed together with the patient at least annually.

- The patient must be fully informed and understand the 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, or if she becomes pregnant or thinks she may be pregnant and is taking topiramate

- As a risk minimisation measure, a Pregnancy Prevention Programme should be implemented in women of childbearing potential consisting of the following elements:

    - performance of a pregnancy test before initiating treatment with topiramate;

    - counselling about the risks of topiramate treatment and the need for highly effective contraception throughout treatment and for at least 4 weeks after stopping topiramate treatment;

- 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 form at the beginning of treatment, at each annual review, and if the patient is planning to conceive or has become pregnant;
- ensured 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.

Advice to be given to patients by healthcare professionals

Healthcare professionals should warn women of childbearing potential of the following:

- Taking topiramate while pregnant can cause a serious harm to an unborn child.
- Always use highly effective contraception during your treatment with topiramate.
- If you become pregnant while taking topiramate, do not stop taking this medicine but talk to your doctor immediately.
- It is important to visit your doctor to review your treatment at least once each year.

References

1. Prescribing information of Toplep (Topiramate), Ranbaxy Pharmaceuticals (Pty) Ltd, Roodepoort, May 2022.
2. Important safety information-Topamax (Topiramate) assessed online from https://www.epilepsy.ie/sites/www.epilepsy.ie/files/important-safety-information---topamax-%28topiramate%29.pdf
3. PRAC recommends new measures to avoid topiramate exposure in pregnancy assessed online from https://www.ema.europa.eu/en/news/prac-recommends-new-measures-avoid-topiramate-exposure-pregnancy

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 companies below, or to SAHPRA via the eReporting 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-quality-problem-reportingform/ and email it to adr@sahpra.org.za . Additionally, reporting can be done via the Med Safety App. The App can be downloaded into a smart mobile phone through Google Play or App store. For more information on Med Safety App, please visit the SAHPRA website. For more information on ADR reporting of products listed below, please contact the SAHPRA Vigilance unit at pvqueries@sahpra.org.za or alternatively use the contact details indicated below

Company contact points

Company	Product name	Active ingredient	Registration Number	Contact details
Ranbaxy Pharmaceuticals (Pty) Ltd	Toplep 25	Topiramate	A40/2.5/0348	Geeta Ghela: Geeta.Ghela@sunpharma.com Tel: +27 11 495 0100
	Toplep 50	Topiramate	A40/2.5/0349	
	Toplep 100	Topiramate	A40/2.5/0350	
	Toplep 200	Topiramate	A40/2.5/0351	
Zydus Healthcare SA (Pty) Ltd	Topiramate sprinkles 25	Topiramate	A 42/2.5/0453	Madhu B Swarna: medicinesafety@zydus.co.za Tel: +27 12 748 6400
	Epitoz25	Topiramate	A 41/2.5/0711	
	Epitoz50	Topiramate	A 41/2.5/0712	
	Epitoz100	Topiramate	A 41/2.5/0713	
	Topiramate 25 Unicorn	Topiramate	A 42/2.5/0277	
	Topiramate 50 Unicorn	Topiramate	A 42/2.5/0278	
	Topiramate 100 Unicorn Zydus	Topiramate	A 42/2.5/0279	
Trinity Pharma (Pty) Ltd	Epimate 25	Topiramate	43/2.5/0823	Shamillah Holland: shamillah.holland@trinitypharma.co.za pv@trinitypharma.co.za Tel: +27 10 594 5610
	Epimate 50	Topiramate	43/2.5/0824	
	Epimate 100	Topiramate	43/2.5/0825	
	Epimate 200	Topiramate	43/2.5/0826	

Yours faithfully,

Geeta Ghela Responsible Pharmacist Ranbaxy Pharmaceuticals (Pty) Ltd a Sun Pharma Company Signature	Madhu B Swarna Responsible Pharmacist Zydus Healthcare SA (Pty) Ltd Signature	Shamillah Holland Responsible Pharmacist Trinity Pharma (Pty)Ltd Signature