Johnson&Johnson

Janssen-Cilag Pty Ltd
507 Mount Wellington Highway
Mount Wellington, Auckland 1060

P 0800 800 806
www.jnj.com

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TOPAMAX® (Topiramate):
New restrictions to prevent exposure during pregnancy

Dear Healthcare Professional,

Janssen-Cilag Pty Ltd (a Johnson & Johnson Company), in consultation with Medsafe, would like to inform you of the implementation of the pregnancy prevention measures for topiramate-containing medicinal products.

Summary

- Topiramate can cause major congenital malformations and fetal 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.
- Topiramate for prophylaxis of migraine is already contraindicated in pregnancy and in women of childbearing potential not using highly effective contraception.
- 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.
- 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.
- Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In treating and counseling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks and consider alternative therapeutic options. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Background on the safety concern

Indications:

EPILEPSY
TOPAMAX is indicated in adults and children, 2 years and over:

- as monotherapy in patients with newly diagnosed epilepsy
- for conversion to monotherapy in patients with epilepsy
- as add-on therapy in partial onset seizures, generalised tonic-clonic seizures or seizures associated with Lennox-Gastaut syndrome.

MIGRAINE
TOPAMAX is indicated in adults for the prophylaxis of migraine headache. The usefulness of TOPAMAX in the acute treatment of migraine headache has not been studied.

Please refer to the TOPAMAX® Data Sheet for complete prescribing information, available from the Janssen website (www.janssen.com/newzealand/our-medicines).

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- 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[3] 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.

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%).[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.[5]
- A higher prevalence of low birth weight (< 2500 grams) compared with a reference group.[6]
- 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.[6]

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

<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, respectively.
- Alternative therapeutic options should be considered.
- The need for topiramate treatment in these populations should be reassessed at least annually.

<u>In women of childbearing potential:</u>

- Topiramate for migraine prophylaxis is contraindicated:
  - in pregnancy,
  - 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 JanssenPro website (www.janssenpro.co.nz/AuthHome/Products/TOPAMAX). Patients can access an electronic copy of the patient guide at url.janssenap.com/TopiramateNZpatientguide

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

Please refer to the TOPAMAX® Data Sheet for complete prescribing information, available from the Janssen website (www.janssen.com/newzealand/our-medicines).

Adverse Event Reporting

Janssen is committed to monitoring the safety of our products. We encourage HCPs to report any suspected adverse events and other safety information for TOPAMAX® to Medsafe at (www.medsafe.govt.nz/safety/report-a-problem.asp) and/or Janssen's Medical Information Department.

If you have further questions, please contact Janssen Medical Information on 0800 800 806 or medinfo@janau.jnj.com.

Yours sincerely,

Alessandra Sandrini
Director Medical & Scientific Affairs
Immunology & Specialty
Johnson & Johnson

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.** Hernández-Díaz S, Straub L, Bateman BT, *et al. Risk of Autism after Prenatal Topiramate, Valproate, or Lamotrigine Exposure. N Engl J Med.* 2024 Mar 21;390(12):1069-1079. doi: 10.1056/NEJMoa2309359. PMID: 38507750; PMCID: PMC11047762. **4.** The North American Antiepileptic Drug Pregnancy Registry https://www.aedpregnancyregistry.org/ **5.** Cohen JM, Alvestad S, Cesta CE, *et al. Comparative Safety of Antiseizure Medication Monotherapy for Major Malformations. Ann Neurol.* 2023; 93(3):551-562.**6.** 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.

TOPAMAX® (TOPIRAMATE) MINIMUM DATA SHEET

TOPAMAX® is a funded medicine – restrictions apply. For further details, see https://pharmac.govt.nz/pharmaceutical-schedule.

INDICATIONS: Epilepsy: TOPAMAX is indicated in adults and children, 2 years and over: as monotherapy in patients with newly diagnosed epilepsy; for conversion to monotherapy in patients with epilepsy and as add-on therapy in partial onset seizures, generalised tonic-clonic seizures or seizures associated with Lennox-Gastaut syndrome. **Migraine:** TOPAMAX is indicated in adults for the prophylaxis of migraine headache. The usefulness of TOPAMAX in the acute treatment of migraine headache has not been studied. **DOSAGE AND ADMINISTRATION: Epilepsy:** For optimum seizure control in both adults and children, it is recommended that therapy should be initiated at a low dose followed by slow titration to an effective dose. Dose titration should be guided by clinical outcome, as outlined below.

Table 1: Recommended dosages in adults and children

		Monotherapy	Add-on therapy
Adults	**Starting dose**	25 mg as a single (nightly) dose for one week (or longer).	25 to 50 mg as a single (nightly) or divided dose for one week (or longer).
	Escalation dose	Increase by 25 to 50 mg/day at weekly or longer intervals.	Increase by 25 to 100 mg/day at weekly or longer intervals.
	Target dose	100 mg/day	200 to 400 mg/day
	Maximum dose	Up to 500 mg/day[1]	Up to 1000 mg/day
Children 2 years & over	**Starting dose**	0.5 to 1 mg/kg as a single (nightly) dose for the first week.	1 to 3 mg/kg/day up to 25 mg/day as a single (nightly) dose for the first week.
	Escalation dose	Increase by 0.5 to 1 mg/kg/day at weekly or longer intervals.	Increase by 1 to 3 mg/kg/day at weekly or longer intervals.
	Target dose	3 to 6 mg/kg/day	5 to 9 mg/kg/day
	Maximum dose	Up to 500 mg/day	Up to 30 mg/kg/day

Note: Daily doses greater or equal to 50 mg should be taken as two divided doses.
[1]Some patients with refractory epilepsy have tolerated doses of 1000 mg/day.)

Migraine: Adults: Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased weekly in increments of 25 mg/day. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used. The recommended total daily dose of TOPAMAX as treatment for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. Dose and titration should be guided by clinical outcome. See full Data Sheet for instructions for use. **CONTRAINDICATIONS:** Hypersensitivity to any component of this product. Migraine prophylaxis in pregnancy and in women of childbearing potential if not using a highly effective method of contraception. **PRECAUTIONS:** Withdrawal of TOPAMAX, nephrolithiasis, hydration, serious skin reactions, suicidality (suicidal behaviour and ideation), rapid dose reduction, discontinuation or substitution of TOPAMAX, oligohydrosis and hyperthermia, decreased hepatic function, acute myopia and secondary angle closure glaucoma syndrome, visual field defects, metabolic acidosis and sequelae, hyperammonemia and encephalopathy, mood disturbances/depression, suicide attempt, women of childbearing potential/ pregnancy, nutritional supplementation, decreased renal function, elderly and breastfeeding. **INTERACTIONS:** Phenytoin, carbamazepine, digoxin, CNS depressants, contraceptives, lithium, risperidone, hydrochlorothiazide, metformin, pioglitazone, glibenclamide, agents predisposing to nephrolithiasis, valproic acid, vitamin K-antagonist anticoagulant medications, amitriptyline, haloperidol, propranolol, diltiazem, flunarizine. Others see full Data Sheet. **ADVERSE EFFECTS:** somnolence, dizziness, fatigue, irritability, weight decreased, bradyphrenia, paraesthesia, diplopia, coordination abnormal, nausea, nystagmus, lethargy, anorexia, dysarthria, vision blurred, decreased appetite, memory impairment, diarrhoea, disturbance in attention, aggression, rash, abnormal behaviour, balance disorder, constipation, depression, anxiety, asthenia, dysgeusia, hypoesthesia, pyrexia, alopecia, insomnia, and expressive language disorder. Others see full Data Sheet. **MEDICINE CLASSIFICATION:** Prescription Medicine **PRESENTATION:** Each TOPAMAX tablet contains 25, 50, 100 or 200 mg of topiramate. Each TOPAMAX Sprinkle Capsule contains 15, 25 or 50 mg of topiramate. Before prescribing, please review full Data Sheet available from https://www.janssen.com/newzealand/sites/www_janssen_com_newzealand/files/prod_files/live/topamax_data_sheet.pdf or www.medsafe.govt.nz. Janssen-Cilag (New Zealand) Ltd, 507 Mount Wellington Hwy, Mount Wellington, Auckland 1060, New Zealand. Date of Preparation: 6 November 2024 Material Preparation Date: January 2025. CP-487536. TAPS BC4764. JANS5508/EMBC.