HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

janssen
PHARMACEUTICAL COMPANIES OF
Johnson&Johnson

Topamax▼ (topiramate)
Pregnancy Prevention Programme

Guide for Healthcare Professionals who manage girls and women of childbearing potential treated with topiramate

Information on use of topiramate in accordance with the Pregnancy Prevention Programme

Please read this guide and the current version of the Summary of Product Characteristics before any prescription of topiramate to girls and women of childbearing potential.

Electronic copies of this Guide and other materials related to the topiramate Pregnancy Prevention Programme can also be found online at www.hpra.ie. Enter «Topamax» or «topiramate» in the search box and then click on «EdM» next to any of the medicines that appear.

Electronic copies of this Guide and other materials related to the topiramate Pregnancy Prevention Programme can also be found online at www.medicines.ie.

This Guide has been approved by the Health Products Regulatory Authority

Table of Contents

1. Purpose of this guide

Topiramate use during pregnancy is harmful for the unborn child. Children exposed in utero have a higher risk for congenital malformations, low birth weight and being small for gestational age (SGA). There may also be an increased risk for neurodevelopmental disorders.

See Chapter 6 for more information.

Topiramate educational tools have been developed specifically for healthcare professionals and for girls, adolescents and women of childbearing potential treated with topiramate. These tools include:

- This Healthcare Professional Guide
- An Annual Risk Awareness Form
- A Patient Guide
- A Patient Card

The objective of this Healthcare Professional Guide is to provide healthcare professionals involved in the patient journey with information about:

- The prescribing conditions in girls and women of childbearing potential.
- The teratogenic and neurodevelopmental risks with the use of topiramate during pregnancy.
- The actions necessary to minimise the risks.

For patients who are minors or without the capacity to make an informed decision, provide the information to their parents/legal guardian/caregiver and make sure they clearly understand it.

Please read the most up-to-date version of the Summary of Product Characteristics before prescribing topiramate.

2. Conditions of topiramate prescription in girls and women of childbearing potential: Actions for Doctors

Treatment of girls (epilepsy) and women of childbearing potential (epilepsy and migraine) with topiramate should be initiated and supervised by a physician experienced in the management of epilepsy or migraine.

Alternative therapeutic options should be considered.

The need for topiramate treatment in these populations should be reassessed at least annually.

Please see below table summarising the contraindications to topiramate prescription in pregnancy and women of childbearing potential.

	The patient has	
	Epilepsy (from menarche to menopause)	**Migraine prophylaxis** (adult women)
She is of childbearing potential	Do not prescribe unless the patient is using highly effective contraception. Only exception: a woman for whom no suitable alternative exists but who plans pregnancy and is fully informed about the risks.	Do not prescribe unless the patient is using highly effective contraception.
She is pregnant	Do not prescribe unless there is no suitable alternative treatment.	Do not prescribe.

Table 1: Summary of the contraindications for the prescribing of topiramate in pregnancy and women of childbearing potential for the treatment of epilepsy and prophylaxis of migraine.

In women of childbearing potential

- Consider if there are other suitable treatment options.
- If you decide to prescribe topiramate, ensure that your patient is fully informed of and understands the risks related to topiramate use during pregnancy.
- Perform a pregnancy test prior to treatment initiation to rule out existing pregnancy.
- Counsel your patient on the need for highly effective contraception throughout the treatment and at least 4 weeks after treatment discontinuation. Guidance on contraceptive methods should be provided (see section below ***Contraception***).
- Advise your patient to immediately contact you if she has become pregnant or thinks she might be pregnant (see section below ***If your patient has become pregnant while treated with topiramate***)
- Advise your patient to contact you as soon as she is planning a pregnancy and before she stops her contraception so that she can discuss switching to alternative treatments before she becomes pregnant (see section below ***Pregnancy planning***).
- Reassess and discuss the need for and risks of topiramate treatment during pregnancy with your patient if she is planning a pregnancy, becomes pregnant and at least once a year during treatment.
- Provide the Patient Guide to your patient and complete the Annual Risk Awareness Form with her at treatment initiation and/or at her annual reassessment, in the event of pregnancy planning or if the patient becomes pregnant.
- **Patients with epilepsy:** fully inform your patient about the risks of untreated epilepsy to her and the unborn child.

Contraception

- Counsel on the need for highly effective contraception throughout the treatment and at least 4 weeks after treatment discontinuation.
- Guidance on contraceptive methods should be provided.
- 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.
- Inform your patient about the possibility of decreased contraceptive efficacy and increased breakthrough bleeding if taking systemic hormonal contraceptives products with topiramate. Advise your patient to report any change in their bleeding patterns to you. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding. Women using systemic hormonal contraceptives should add a barrier method.

2.1 Pregnancy planning

In patients with epilepsy:

- Explain the need for pregnancy planning.
- Promptly arrange a specialist review to reassess topiramate treatment and consider alternative treatment options.
- Explain that, where possible, contraception should only be stopped after complete topiramate cessation.
- Inform your patient and her partner about the risks:
  - to the unborn child exposed to topiramate in utero
  - of untreated epilepsy during pregnancy
- Tell your patient to continue topiramate until the date of the appointment with her specialist.
- Ensure she has the Patient Guide.
- Advise your patient that she should contact you immediately if she has become pregnant or thinks she might be pregnant.

In patients with migraine:

- Explain the need for pregnancy planning.
- Reassess topiramate treatment and switch to alternative treatment before contraception is discontinued.
- Inform your patient and her partner about the risks to the unborn child exposed to topiramate in utero.
- Consider the need for specialist referral if required.
- Complete the Annual Risk Awareness Form.
- Provide the Patient Guide.

2.2 If your patient has become pregnant while treated with topiramate

In patients with epilepsy

- Urgently arrange specialist review (i.e. within days) to reassess topiramate treatment and consider alternative treatment options.
- Inform your patient to keep taking her treatment until her next consultation due to the risk of breakthrough seizures having serious consequences for the woman and the unborn child.
- Inform your patient and her partner about the risks:
  - to the unborn child exposed to topiramate in utero
  - of untreated epilepsy during pregnancy
- Provide the Patient Guide.

In patients with migraine:

- Stop treatment with topiramate immediately.
- Inform your patient and her partner about the risks to the unborn child exposed to topiramate in utero.
- Consider the need for specialist referral if required.
- Refer your patient to an obstetrician for prenatal monitoring and counselling.
- Complete the Annual Risk Awareness Form.
- Provide the Patient Guide.

2.3 Managing a girl with epilepsy treated with topiramate

- Explain the risks due to topiramate use during pregnancy to the parents/legal guardian and the girl depending on her age.
- Explain the importance of contacting you to arrange specialist review once menarche is reached.
- Assess the most appropriate time to give advice on contraception.
- Provide the Patient Guide.

3. Conditions of topiramate prescription in girls and women of childbearing potential: Specific Actions for Specialists (Epilepsy Indication)

A woman with epilepsy being treated with topiramate and planning for pregnancy should be referred for specialist consultation.

Urgent referrals (i.e. within days) should be arranged in case of a patient that has become pregnant or thinks she may be pregnant and is taking topiramate for epilepsy.

Girls taking topiramate should also be reviewed by a specialist at the time of menarche.

A specialist is defined as a consultant neurologist who regularly manages complex epilepsy.

See below for further details.

3.1 Pregnancy planning

- Reassess topiramate treatment. If possible, switch to alternative treatment before contraception is discontinued.
- Explain to your patient that the switch to alternative treatment in epilepsy takes time. Switching to an alternative treatment should be undertaken in accordance with clinical practice and available guidelines, as appropriate.
- Inform your patient and her partner about the risks:
  - to the unborn child exposed to topiramate in utero
  - of untreated epilepsy to the pregnancy
- Advise your patient to contact you immediately if she has become pregnant or thinks she might be pregnant.
- Complete the Annual Risk Awareness Form.
- Provide the Patient Guide.

3.2 If a patient has become pregnant while treated with topiramate

- Reassess topiramate treatment and consider alternative treatment options.
- Inform your patient and her partner about the risks:
  - to the unborn child exposed to topiramate in utero
  - of untreated epilepsy to the pregnancy
- Refer your patient to an obstetrician for counselling and careful prenatal monitoring.
- Complete the Annual Risk Awareness Form.
- Provide the Patient Guide.

During pregnancy topiramate should preferably be prescribed:

- as monotherapy,
- at the lowest effective dose.

3.3 Managing a girl with epilepsy treated with topiramate

- Make every effort to switch girls to alternative treatment before menarche is reached.
- Explain the risks due to topiramate use during pregnancy to the parents/legal guardian and the girl depending on her age.
- Explain the importance of contacting you once a girl experiences menarche.
- At a consultation with a girl that has reached menarche:
  - Reassess topiramate treatment and consider alternative treatment options.
  - Explain the risks due to topiramate use during pregnancy to the parents/legal guardian and the girl depending on her age, and about the need to use highly effective contraception as soon as it is relevant.
  - Complete the Annual Risk Awareness Form.
  - Provide the Patient Guide.

4. Conditions of topiramate prescription in girls and women of childbearing potential: Actions for Gynaecologists/Obstetricians

In epilepsy, topiramate is contraindicated during pregnancy unless there is no suitable alternative treatment.

In migraine, topiramate is contraindicated during pregnancy.

If a patient has become pregnant while treated with topiramate:

In patients with epilepsy

- Urgently refer your patient to a neurologist.
- Sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. If topiramate has been or is used during pregnancy, your patient should be counselled and careful prenatal monitoring should be performed.
- Provide the Patient Guide.

In patients with migraine:

- Stop treatment with topiramate immediately.
- Consider the need for neurologist referral if required.
- If topiramate has been used during pregnancy, your patient should be counselled and careful prenatal monitoring performed.
- Provide the Patient Guide.

5. Conditions of topiramate prescription in girls and women of childbearing potential: Actions for Pharmacists

Topiramate is contraindicated in the following conditions:

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.

Prophylaxis of migraine:

- in pregnancy.
- in women of childbearing potential not using highly effective contraception.

Remind and ensure patient's understanding of:

- The higher risk of congenital malformations, low birth weight and being small for gestational age (SGA) and the possibility of an increased risk of neurodevelopmental disorders.
- The need for highly effective contraception during treatment and for at least 4 weeks after stopping treatment.
- The need to plan for pregnancy and reassess treatment with her doctor at least annually.

Educational materials

- **Patient Card:** Provide a copy or ensure your patient received it in the box. Discuss its contents every time topiramate is dispensed. Advise your patient to keep it with them.
- **Patient Guide:** Ensure your patient received it.
- **Online information:** Remind your patient that online information can also be found by scanning the QR code which is included in the patient leaflet and on the patient card.

Dispense topiramate in the original package with an outer warning. Dispensing outside of original packaging should be avoided. In situations where this cannot be avoided, always provide a copy of the package leaflet, patient card and add a sticker with the warning to the outer packaging.

6. What are the risks of taking topiramate during pregnancy?

Topiramate is teratogenic. Children exposed in utero to topiramate have a higher risk for congenital malformations, low birth weight and being small for gestational age (SGA).

There may also be an increased risk for neurodevelopmental disorders.

6.1 Congenital malformations

- In the North American Antiepileptic Drug pregnancy registry about 4.3% of children exposed to topiramate monotherapy had a major congenital malformation compared to 1.4% in a reference group not taking antiepileptic drugs (AEDs).
- The most common types of malformation included: cleft lip and cleft palate, hypospadias and anomalies involving various body systems.
- A population-based registry study from the Nordic countries also showed a **2 to 3 fold higher prevalence of major congenital malformations (up to 9.5 %), compared with a reference group not taking AEDs (3.0%)**.
- 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; adverse effects were observed even with low doses.

6.2 Foetal growth restriction

- A higher prevalence of low birth weight (<2500 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) was found in topiramate exposed children compared with a reference group. In the North American Antiepileptic Drug Pregnancy Registry**, the risk of SGA in children of women receiving topiramate was 18%, compared with 5% for women without epilepsy not receiving an antiepileptic drug. The long-term consequences of the SGA findings could not be determined**.

6.3 Neurodevelopmental disorders

- Data from two observational population-based registry studies 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 AED.
- A third observational cohort study from the U.S.A. did not suggest an increased prevalence of these outcomes 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.

▼ This medicinal product is subject to additional monitoring and it is therefore important to report any suspected adverse events related to this medicinal product. Healthcare professionals are asked to report suspected adverse events via: HPRA Pharmacovigilance, Website: www.hpra.ie.

Adverse events should also be reported to Janssen Sciences Ireland UC on 0044(0)1494 567447 or email dsafety@its.jnj.com. By reporting side effects you can help provide more information on the safety of this medicine.

ADHD, attention deficit hyperactivity disorder; AEDs, antiepileptic drugs; SGA, small for gestational age; WCBP, Women of Childbearing Potential.

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