Topiramate▼ Pregnancy Prevention Programme

Healthcare Professional Guide

Prophylaxis of migraine

▼ *This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.*

Information on the risks of topiramate use in women of childbearing potential in the treatment of prophylaxis of migraine

Purpose of this Guide

Read this Guide carefully before prescribing topiramate to women of childbearing potential. It is part of the topiramate Pregnancy Prevention Programme, which is aimed at minimising pregnancy exposure during treatment with topiramate.

It provides up-to-date information about the risks of serious **congenital malformations, neurodevelopmental disorders and effects on fetal growth** in children of mothers exposed to topiramate during pregnancy. It also describes the actions necessary to minimise the risks to your patients, and to ensure your patient has an adequate understanding of the risk.

The other educational materials developed for women of childbearing potential treated with topiramate comprise:

- The Patient Guide
- The Annual Risk Awareness From
- The Patient Card

Use this Healthcare Professional Guide together with the Patient Guide.

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Implementing the topiramate Pregnancy Prevention Programme

Topiramate is an effective treatment for prophylaxis of migraine.

Topiramate should not be used in women of childbearing potential unless they follow the requirements of the Pregnancy Prevention Programme.

A woman of childbearing potential is a pre-menopausal female (from menarche to menopause) who can become pregnant.

Topiramate is contraindicated in:

- pregnancy
- women of childbearing potential unless the conditions of the topiramate Pregnancy Prevention Programme (outlined below) are fulfilled.

The conditions of the Pregnancy Prevention Programme need to be maintained throughout the period of use of topiramate. This includes patients who are switching to a therapy other than topiramate – the conditions of the Pregnancy Prevention Programme should be continued until topiramate is discontinued.

Actions for healthcare professionals initiating or reviewing topiramate treatment

Initiating topiramate in women of childbearing potential

- Assess potential for pregnancy and, if necessary, discuss the need for her to be on the Pregnancy Prevention Programme if she is to take topiramate.
- Discuss the risks with the patient and ensure they understand the:
  - possible therapeutic options available
  - risks to the unborn child if topiramate is taken during pregnancy
  - the need to take highly effective contraception throughout treatment and undergo pregnancy testing when required – e.g. if there is any reason to suggest lack of compliance or effectiveness of contraception
  - the need to contact you urgently if they suspect they might be pregnant or wish to plan a pregnancy
- Before the first prescription is issued in women of childbearing potential:
  - Exclude pregnancy (by serum pregnancy test)
  - Arrange for highly effective contraception (see 'Contraception' section below)
- Complete the Annual Risk Awareness Form with the patient and give them a copy..
- Provide a copy of the Patient Guide to the patient.
- See the patient promptly in case of unplanned pregnancy or if she wants to plan a pregnancy.

Annual review

- Invite all female patients on the topiramate Pregnancy Prevention Programme for an annual review.
- Continue treatment with topiramate only if the conditions of the Pregnancy Prevention Programme are fulfilled.
- Make sure all patients have an up to date, signed, Annual Risk Awareness Form.
- Ensure continuous use of highly effective contraception in all women of childbearing potential (consider the need for pregnancy testing if not a highly effective method).
- Ensure she has the Patient Guide and has a copy of her up to date Annual Risk Awareness Form.

Women planning to become pregnant or with an unplanned pregnancy

- Ensure they understand the risks of topiramate in pregnancy.
- Discontinue topiramate in **women planning a pregnancy.** Migraine often improves in pregnancy, typically during the second and third trimesters. Therefore, women do not usually need preventative treatment during pregnancy.
- The conditions of the Pregnancy Prevention Programme continue to apply until the topiramate has been discontinued. Ask her not to stop contraception until she has no longer been taking topiramate for at least a month.
- Women with migraine presenting with an **unplanned pregnancy** should have their treatment discontinued.

Actions for community pharmacy team and dispensing practice team

- Ensure that the:
  - Patient Card is provided every time topiramate is dispensed
  - patient has received the Patient Guide
- Remind patients of the
  - risks in pregnancy
  - the need to use highly effective contraception throughout treatment with topiramate
  - need for annual review
- If topiramate is not dispensed in the original package, provide a copy of the package leaflet and add a sticker with the warning to the outer box.
- If a woman of childbearing potential is not aware of the need for contraception and has not been seen by her prescriber in the past year, dispense their medicine and refer them to their prescriber (including by contacting the prescriber if necessary).

Actions for gynaecologists/obstetricians, midwives and nurses

- Provide counselling on contraception methods and pregnancy planning.
- Provide information about the risks of using topiramate during pregnancy.
- When a patient consults for pregnancy refer her and her partner to her prescriber and to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Contraception

Women of childbearing potential taking topiramate should be using at least one highly effective method of contraception (preferably a user independent form such as a copper intrauterine device (Cu-IUD) or levonorgestrel intrauterine system (LNG-IUS)) or two complementary forms of contraception including a barrier method throughout treatment.

Involve the patient in the discussion about the most appropriate contraceptive method to guarantee her engagement and compliance with the chosen measures. Ensure that she understands that even if she has amenorrhoea she must follow all the advice on highly effective contraception.

Consider the possibility of decreased contraceptive efficacy and increased breakthrough bleeding in patients taking systemic hormonal contraceptive products with topiramate.

Women using systemic hormonal contraceptives should also use a barrier method. Ask them to report any change in their bleeding patterns; contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

Further information on the potential for drug interactions with hormonal contraceptives is provided in the Faculty of Family Planning and Sexual Health guidance[7].

Risks related to topiramate use during pregnancy

Topiramate is teratogenic. Children exposed in utero to topiramate have a higher risk for congenital malformations and neurodevelopmental disorders and also a higher prevalence of low birth weight and being born small for gestational age[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 antiseizure medication[1].

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[2] also showed a 2 to 3-fold higher prevalence of major congenital malformations (up to 9.5 %), compared with a reference group not taking antiseizure medication (3.0%).

Studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of antiseizure medication in combination therapy. The risk has been reported to be dose dependent; adverse effects were observed even with low doses[1].

Developmental disorders

Data from two observational population-based registry studies[3,4] 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 antiseizure medication.

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 antiseizure medication[5].

Fetal 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[1].

In the North American Antiepileptic Drug Pregnancy Registry[6], the risk of SGA in children of women receiving topiramate was 18%, compared with 5% for women without epilepsy not receiving an antiseizure medication.

1. EMC Topiramate page https://www.medicines.org.uk/emc/search?q=Topiramate

2. Cohen JM, Alvestad S, Cesta CE, et al. Comparative Safety of Antiseizure Medication Monotherapy for Major Malformations. Ann Neurol. 2023; 93(3):551-562

3. Bjørk M, Zoega H, Leinonen MK, et al. Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. JAMA Neurol. 2022; 79 (7): 672-682.

4. Dreier JW, Bjørk M, Alvestad S, et al. Prenatal Exposure to Antiseizure Medication and Incidence of Childhood- and Adolescence-Onset Psychiatric Disorders. JAMA Neurol. 2023; 80 (6): 568 – 577.

5. 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.

6. North American Antiepileptic Drug Pregnancy Registry https://www.aedpregnancyregistry.org/

7. https://www.fsrh.org/standards-and-guidance/documents/ceu-clinical-guidance-drug-interactions-with-hormonal/

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