Topiramate▼ Pregnancy Prevention Programme

Healthcare Professional Guide

Epilepsy

▼ *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 girls (of any age) and women of childbearing potential in the treatment of epilepsy.

Purpose of this Guide

Read this Guide before prescribing topiramate to female patients.

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.

It is recommended that pregnant women taking antiseizure medications, including topiramate, are enrolled in the UK Epilepsy and Pregnancy Register (http://www.epilepsyandpregnancy.co.uk). This should be done as early as possible in the pregnancy, before the outcome is known.

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

- The Patient Guide
- The Annual Risk Awareness Form, and
- 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 epilepsy.

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 unless there is no suitable alternative
- women of childbearing potential unless the conditions of the topiramate Pregnancy Prevention Programme (outlined below) are fulfilled.

Actions for specialist prescribers

Initiating topiramate in female patients

- Only start treatment with topiramate if pregnancy has been excluded by means of a negative pregnancy test.
- 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 (or parent/caregiver/responsible person) and ensure they understand the:
  - possible therapeutic options available
  - risks to the unborn child if topiramate is taken during pregnancy
  - the need to use 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
- Complete the Annual Risk Awareness Form with the patient (or parent/caregiver/responsible person); give them a copy and, send a copy to the GP.
- Ensure continuous use of highly effective contraception in all women of childbearing potential – see further information in 'Contraception' section below. Refer for contraception services as needed.
- Provide a copy of the Patient Guide to the patient (or parent/caregiver/responsible person).
- See the patient urgently (within days) if referred back 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. Send a copy to the GP.

Women planning to become pregnant

- Ensure that she understands the risks of topiramate in pregnancy.
- Switch topiramate to another therapeutic option. The conditions of the Pregnancy Prevention Programme continue to apply until the switch from topiramate is complete.
- Ask her not to stop contraception until the switch is achieved and she has no longer taking been taking topiramate for at least a month.
- If switching is not possible refer for counselling about the risks.

Patients with an unplanned pregnancy

- Women presenting with an unplanned pregnancy should have their treatment switched.
- Women who must continue treatment in pregnancy (i.e. if switching to an alternative treatment is not possible) should be referred for appropriate monitoring.

Actions for General Practice team

- Ensure continuous use of highly effective contraception in all women of childbearing potential.
- Check that all patients on the topiramate Pregnancy Prevention Programme have an up to date, signed, Annual Risk Awareness Form when a repeat prescription is issued.
- Remind all female patients that they will need to see their specialist at least once every year while taking topiramate.
- Refer to the specialist urgently (within days) in case of unplanned pregnancy. Inform her not to stop taking topiramate until told to do so by her specialist.
- Refer any female patient planning to become pregnant to the specialist. Inform her not to stop using contraception or topiramate until told to do so by her specialist.

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 specialist in the past year, dispense their medicine and refer them to their GP (including by contacting the GP 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].

Switching or discontinuing topiramate

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess topiramate therapy. Every effort to be made to switch to alternative treatment options prior to conception and before contraception is discontinued.

The conditions of the Pregnancy Prevention Programme continue to apply until the switch from topiramate is complete.

If a woman becomes pregnant on topiramate, she must be immediately referred to a specialist.

General consideration of patients with epilepsy switching treatment

Topiramate should be gradually withdrawn over weeks to months to minimise the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were decreased in weekly intervals by 50-100 mg in adults with epilepsy.

The switch of topiramate to an alternative treatment will commonly occur over at least 2–3 months. The new medication is usually gradually introduced as add on to topiramate. This can take up to 6 weeks to reach a potentially effective dose of the new treatment; thereafter an attempt can be made to gradually withdraw topiramate.

If, despite the known risks of topiramate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive topiramate for epilepsy:

- There is no dose threshold considered to be without any risk. However, the risk of fetal growth restriction, birth defects and developmental disorders appears to be higher at greater doses.
- Use the lowest effective dose of topiramate administered in two divided doses.
- All patients with a topiramate exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine.

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.

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 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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