13 October 2023
EMA/455917/2023

New measures to avoid topiramate exposure in pregnancy

Further restrictions on use; pregnancy prevention programme to be put in place

On 11 October 2023, the CMDh[1] endorsed new measures recommended by EMA's safety committee (PRAC) in September to avoid exposure of children to topiramate-containing medicines in the womb, because the medicine may increase the risk of neurodevelopmental problems after exposure during pregnancy. Topiramate is already known to cause serious birth defects when used during pregnancy.

Topiramate-containing medicines are used in the European Union (EU) for the treatment of epilepsy and prevention of migraine. In some EU countries, the medicine is also used in combination with phentermine for weight reduction. At present, topiramate must not be used to prevent migraine or manage body weight during pregnancy and patients who can become pregnant must use effective birth control when using topiramate.

For patients using topiramate for the treatment of epilepsy, the medicine should not be used during pregnancy unless there is no other suitable treatment available.

The CMDh has also agreed to additional measures, in the form of a pregnancy prevention programme, to avoid exposure of children to topiramate in the womb. These measures will inform any woman or girl who is able to have children of the risks of taking topiramate during pregnancy and the need to avoid becoming pregnant while taking topiramate.

Healthcare professionals should ensure that all patients who can become pregnant are fully aware of the risks of taking topiramate during pregnancy. Alternative treatment options should be considered and the need for topiramate treatment should be reassessed at least annually.

The product information for topiramate-containing medicines will be updated to further highlight the risks and the measures to be taken. Patients and healthcare professionals will be provided with educational materials regarding the risks of using topiramate during pregnancy, and a patient card will be provided to the patient with each medicine package. A visible warning will also be added to the outer packaging of the medicine.

[1]The CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

These measures follow a review of available data by the PRAC, including three recent observational studies[2,3,4]. Two of these studies, which used largely the same datasets, suggest that children born to mothers with epilepsy and who were exposed to topiramate in the womb may have a two- to three-fold higher risk of neurodevelopmental disorders, in particular autism spectrum disorders, intellectual disability or attention deficit hyperactivity disorder (ADHD), compared with children born to mothers with epilepsy not taking antiepileptic medication. The third study did not show an increased risk of these outcomes in children born to mothers exposed to topiramate in pregnancy, compared with children born to women with epilepsy not taking antiepileptic medication.

In its review, the PRAC confirmed the known increased risk of birth defects and reduced growth of the unborn child when mothers receive topiramate during pregnancy. Birth defects will occur in 4 to 9 out of every 100 children born to women who take topiramate during pregnancy, compared with 1 to 3 out of every 100 children born to women who do not take such treatment. Further, around 18 in every 100 children were smaller and weighed less than expected at birth when mothers had taken topiramate during pregnancy, compared with 5 in every 100 children born to mothers without epilepsy and not taking antiepileptic medication.

During the review PRAC also consulted a group of experts, patient representatives and specialists.

The companies that market topiramate must carry out a drug utilisation study and surveys of healthcare professionals and patients to assess the effectiveness of the new measures.

Following the adoption of the PRAC recommendations by the CMDh, these measures will now be implemented in all Member States where topiramate-containing medicines are authorised.

Information for patients

- Exposure to topiramate in the womb can cause birth defects in children, and exposed newborns may be smaller and weigh less than expected at birth. Exposure to topiramate in the womb may also increase the risk of problems with the development of brain function, such as autism spectrum disorders, intellectual disability or attention deficit hyperactivity disorder (ADHD).
- If you are pregnant or able to become pregnant, there are important restrictions on the use of topiramate:
  - you must not use topiramate to prevent migraine or manage your body weight if you are pregnant. If you can become pregnant, you must not use topiramate for these conditions unless you are using highly effective birth control.
  - if you have epilepsy, you must not use topiramate if you are pregnant unless there are no other treatments that give you sufficient control of seizures.
  - if you have epilepsy and can become pregnant, you must not use topiramate unless you are using highly effective birth control. If you are planning to become pregnant and topiramate is the only treatment giving you sufficient seizure control, you should speak to your doctor, who

[2] 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 Jul 1;79(7):672-681. doi: 10.1001/jamaneurol.2022.1269.
[3] 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 Jun 1;80(6):568-577. doi: 10.1001/jamaneurol.2023.0674.
[4] Hernandez-Diaz S, Straub L, Bateman B, et al. Topiramate During Pregnancy and the Risk of Neurodevelopmental Disorders in Children. 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.

will give you information about the risks of taking topiramate during pregnancy and about the risks of seizures during pregnancy.

- If you are a patient who can become pregnant, your doctor will provide you with information so you will understand the risks of taking topiramate during pregnancy. This will be done before you start taking topiramate and at least once every year during treatment.
- If you can become pregnant, you should always use an effective method of birth control while taking topiramate. Talk to your doctor about which contraceptive method is right for you while you are taking topiramate.
- Talk to your doctor if you are planning to become pregnant. Do not stop using effective birth control until you have discussed an alternative treatment with your doctor. If you are taking topiramate for epilepsy, do not stop taking the medicine without consulting your doctor as this could cause harm to you or your unborn child.
- Tell your doctor immediately if you become pregnant or think you may be pregnant.
- If you have any questions or concerns, you should discuss them with your doctor.

Information for healthcare professionals

- It is already well known that topiramate can cause major congenital malformations and foetal growth restriction when used during pregnancy. Recent data also suggest a possibly increased risk of neurodevelopmental disorders following topiramate use during pregnancy.
- In the prevention of migraine and as treatment for weight management, topiramate is contraindicated during pregnancy. Topiramate must be discontinued if the patient becomes pregnant or is planning for a baby. Patients of childbearing potential should use highly effective contraception during treatment and for at least 4 weeks after stopping topiramate treatment.
- In the treatment of epilepsy, topiramate is contraindicated during pregnancy unless there is no suitable treatment alternative. Topiramate is also contraindicated in women of childbearing potential with epilepsy not using highly effective contraception. The only exception is a woman for whom there is no suitable alternative but who is planning a pregnancy and who has been fully informed about the risks of taking topiramate during pregnancy.
- Irrespective of indication, topiramate should be used in women of childbearing potential only when the following conditions of the pregnancy prevention programme are met:
  - a pregnancy test before starting treatment;
  - counselling about the risks of topiramate treatment and the need for highly effective contraception throughout treatment;
  - a review of ongoing treatment at least annually by completion of a risk awareness form. To confirm that appropriate measures have been taken, patients and prescribers will go through this form at the beginning of treatment and at each annual review and if the patient is planning a pregnancy or has become pregnant. It should be ensured that the patient is fully informed and has understood the risks and measures to be taken.
- Topiramate treatment of patients of childbearing potential should be initiated and supervised by a physician experienced in the management of epilepsy or migraine. Treatment with topiramate/phentermine should be handled by a physician experienced in weight management.

Alternative therapeutic options should be considered and the need for treatment should be reassessed together with the patient at least annually. Ongoing treatment should be re-evaluated to confirm that the measures outlined above have been taken.

A direct healthcare professional communication (DHPC) will be sent in due course to healthcare professionals prescribing, dispensing or administering the medicine. The DHPC will also be published on a dedicated page on the EMA website.

More about the medicine

Topiramate is used on its own or together with other medicines to prevent epileptic seizures. The medicine is also used to prevent migraine headaches and, in some EU countries, for weight reduction in a fixed-dose combination with phentermine.

Topiramate is available in the EU under various trade names, including Topamax, Topimax, Epitomax, and several generic medicines. In some EU countries topiramate is available in combination with phentermine as Qsiva.

More about the procedure

The review of topiramate was initiated at the request of the French medicine agency, under Article 31 of Directive 2001/83/EC. This is related to a safety signal review that started in July 2022 and concluded in September 2022.

The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. As topiramate-containing medicines are all authorised nationally, the PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). The CMDh is a body representing the EU Member States as well as Iceland, Liechtenstein and Norway. It is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by consensus, the measures will be directly implemented by the Member States where these medicines are authorised.