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HPRA DRUG SAFETY
NEWSLETTER

113TH EDITION

In this edition

Topiramate: Introduction of a pregnancy prevention programme and new restrictions on use

Key Message

- Topiramate can cause major congenital malformations and foetal growth restriction when used during pregnancy. Recent data also suggest a possible increased risk of neurodevelopmental disorders (NDD) including autism spectrum disorders, intellectual disability, and attention deficit hyperactivity disorder (ADHD) following topiramate use during pregnancy.
- New contraindications apply for the treatment of 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.
- Topiramate for prophylaxis of migraine is already contraindicated in pregnancy and in women of childbearing potential not using highly effective contraception.
- Treatment of women of childbearing potential should be initiated and supervised by a physician experienced in the management of epilepsy or migraine. 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.
- For women of childbearing potential currently using topiramate, treatment should be re-evaluated to ensure that the measures of the pregnancy prevention programme (key elements described below) are followed.

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Background Information

Topiramate is indicated in children, adolescents, and adults in various forms of epilepsy as mono or adjunctive therapy, and in adults for prophylaxis of migraine after careful evaluation of possible alternative treatment options*.

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has recommended new measures to avoid exposure to topiramate during pregnancy in the form of a pregnancy prevention programme (PPP) and further restrictions on use. This follows a review of data suggesting a possible increased risk of neurodevelopmental disorders (NDD), including autism spectrum disorders, intellectual disability, and attention deficit hyperactivity disorder (ADHD) following topiramate use during pregnancy.

As described in Edition 108 of the HPRA Drug Safety Newsletter, the review by the PRAC[1] was initiated following the recent publication of data from observational studies. During the review, the PRAC considered the available observational study data on NDD, as follows:

- Two observational population-based registry studies[2,3], undertaken in largely the same dataset from Nordic countries, suggest there may be a 2- to 3-fold higher prevalence of autism spectrum disorders, intellectual disability, or 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[4] from the U.S.A. did not suggest an increased cumulative incidence of these outcomes by 8 years of age 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.

The PRAC review has also confirmed the well-known increased risk of major congenital malformation (MCM) and foetal growth restriction (low birth weight and small for gestational age) associated with topiramate use during pregnancy:

- Infants exposed to topiramate monotherapy in utero have an approximately 3-fold increased risk of MCMs including cleft lip/palate, hypospadias and anomalies involving various body systems compared with a reference group not exposed to AEDs. Absolute risks of MCMs following topiramate exposure have been reported in the range of 4.3% (1.4% in the reference group) to 9.5% (3% in the reference group)[5].
- Data from pregnancy registries indicated a higher prevalence of low birth weight (<2,500 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) for topiramate monotherapy. In the North American Antiepileptic Drug Pregnancy Registry, the risk of SGA in children of women receiving topiramate was 18%, compared with 5% in children of women without epilepsy not receiving an AED[6].

Based on review of observational data suggesting a possible increased risk of NDD, in addition to the confirmation of the known risks of MCM and foetal growth restriction, the PRAC recommended further restrictions on use of topiramate and the introduction of a pregnancy prevention programme in the EU.

For women of childbearing potential currently using topiramate, treatment should be re-evaluated to ensure that the measures of the pregnancy prevention programme (key elements described below) are followed.

* *Indicated as monotherapy in adults, adolescents, and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures, and as adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalisation or primary generalised tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome. Topiramate is indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Further details on topiramate containing medicines are available at www.hpra.ie.*

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Key elements of the pregnancy prevention programme

In female children and women of childbearing potential:

- Treatment with topiramate should be initiated and supervised by a physician experienced in the management of epilepsy or migraine (use in this indication is for women of childbearing potential only).
- Alternative therapeutic options should be considered.
- The need for topiramate treatment in these populations should be reassessed at least annually.

In women of childbearing potential:

- Topiramate for migraine prophylaxis is contraindicated:
  - In pregnancy.
  - In women of childbearing potential not using highly effective contraception.
- Topiramate for epilepsy is contraindicated:
  - 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.
- 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 pregnancy and for prompt contact with a specialist doctor 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. Due to a potential interaction, 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 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 (for epilepsy only):

- 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.

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Educational Materials

Educational materials will be developed and circulated to assist healthcare professionals and patients in following the pregnancy prevention programme and in avoiding exposure to topiramate during pregnancy.

These will include:

- A guide for HCPs involved in the care of female children and women of childbearing potential.
- A risk awareness form, which must 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.
- A patient card, which should be provided each time the medicine is dispensed. The card will be either included inside the package or attached to the outer packaging.

Educational materials will be made available on the HPRA website (www.hpra.ie) and will be circulated in hard copy by the marketing authorisation holder for topiramate, following approval by the HPRA.

A textual warning and a pictogram on the teratogenic risk will be introduced as an addition to the outer package of all topiramate-containing medicinal products.

A Direct Healthcare Professional Communication (DHPC) to inform healthcare professionals of the outcome of the review will be distributed shortly.

References:

1. *EMA topiramate referral information. https://www.ema.europa.eu/en/medicines/human/referrals/topiramate*
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. Published online May 31, 2022. 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. Published online April 17, 2023. doi: 10.1001/jamaneurol.2023.0674. Online ahead of print. PMID: 37067807.*
4. *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.*
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:28856.*

Valproate (Epilim) – Ongoing review of potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months prior to conception

Key messages

- The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) is currently evaluating the results of a retrospective observational study to assess the risk of neurodevelopment disorders (NDDs), including autism spectrum disorders, as well as congenital abnormalities in children fathered by men taking valproate-containing medicines in comparison to those fathered by men treated with lamotrigine/ levetiracetam.
- Initial results from this study may indicate an increased risk of NDDs in children of men treated with valproate in the three months prior to conception, compared to those treated with lamotrigine or levetiracetam. However, the PRAC has identified important limitations with the data from the study. In addition, errors in the dataset were identified after submission of the study results. The initial findings are therefore subject to change.
- The PRAC has requested the pharmaceutical companies involved to provide re-analyses of corrected data, as well as additional information and additional analyses to address the study limitations, as soon as possible.
- Patients should be advised that they should not stop taking valproate without first consulting their healthcare professional and also to talk to their healthcare professional if they have questions or concerns.
- This update is provided to inform healthcare professionals of the ongoing EMA review. Further updates on this review as well as any recommendations that may arise will be communicated to patients and healthcare professionals, as appropriate.

Background Information

Valproate-containing medicines are indicated for the treatment of epilepsy and bipolar disorder. In 2018, following an EMA review, which resulted in strengthened warnings and measures to prevent valproate exposure via maternal use during pregnancy, pharmaceutical companies that market these medicines were required to conduct a study to investigate the association between paternal exposure to valproate and the risk of NDDs, including autism spectrum disorders, as well as congenital abnormalities in offspring (EUPAS32401).

This retrospective observational study was conducted using data from multiple registry databases in Denmark, Sweden, and Norway. The initial analyses of the data suggest an increased risk of NDDs in children born to men treated with valproate in the three months prior to conception, compared to those born to men treated with lamotrigine or levetiracetam. However, after submitting the study results, the companies who conducted the study informed the PRAC of errors in the Norwegian dataset relevant to the analysis of risk of NDDs, the impact of which is not yet known[1,2]. The PRAC has also identified important limitations of the current data, including questions about the definition of NDDs in the study as well as the specific types of epilepsy the fathers had. These findings are therefore subject to change. The PRAC has requested companies to provide corrected analyses and additional analyses to address study limitations as soon as possible. The PRAC will review the required data as they become available and make an EU-wide recommendation.

With respect to congenital malformations, the study did not suggest an increased risk in children fathered by men treated with valproate in the three months preceding conception in comparison to those fathered by men treated with lamotrigine or levetiracetam.

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This update is provided to inform healthcare professionals of the ongoing EMA review. Patients should be advised that they should not stop taking valproate without first consulting their healthcare professional and to talk to their healthcare professional if they have questions or concerns.

Further updates on this review as well as any recommendations that may arise will be communicated to patients and healthcare professionals, as appropriate.

Healthcare professionals are also reminded that product information* already includes advice that valproate administration may impair fertility in men. The frequency of male infertility with valproate is rare (≥1/10,000 to ≤1/1,000). Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited number of case reports suggest that a strong dose reduction may improve fertility function. However, in some other cases, the reversibility of male infertility was unknown.

The ongoing evaluation of the results of the study on paternal exposure to valproate does not affect the important contraindications, warnings, restrictions, and risk minimisation measures in place to prevent valproate exposure via maternal use during pregnancy. Healthcare professionals are referred to valproate product information and PREVENT educational materials for further details (see http://www.hpra.ie/homepage/medicines/special-topics/valproate-(epilim) for more information on the PREVENT pregnancy prevention programme).

* *The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL). Valproate product information is available from the HPRA website.*

References:

1. *EMA public health communication concerning the ongoing review of data on paternal exposure to valproate. Available at: https://www.ema.europa.eu/en/news/ema-review-data-paternal-exposure-valproate.*
2. *Direct Healthcare Professional Communication sent 15th September concerning the ongoing review of data on paternal exposure to valproate. Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-valproate-(epilim)0ed9142697826eee9b55ff00008c97d0.pdf?sfvrsn=0*

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Systemic and inhaled fluoroquinolone antibiotics - Ciprofloxacin; Delafloxacin; Levofloxacin; Moxifloxacin	Reminder on restrictions of use systemic and inhaled fluoroquinolone antibiotics due to serious and long-lasting adverse reactions
ADAKVEO® (crizanlizumab)	Revocation of EU marketing authorisation due to lack of therapeutic efficacy
Simponi (golimumab) 50 mg and 100 mg	Important changes to the injection instructions for the SmartJect Pre-filled Pen
Valproate (Epilim▾)	Update on the ongoing review of potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months prior to conception

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Reporting suspected adverse reactions

Healthcare professionals are encouraged to report suspected adverse reactions to the HPRA via the available options at http://www.hpra.ie/report, which include an online report form.

All reports submitted to the HPRA are reviewed and stored on the HPRA's national adverse reaction database. They are subsequently submitted to the EMA's EudraVigilance database where they are available for analysis and to support early detection and monitoring of possible safety signals.

Reporting suspected adverse reactions, even those known to occur in association with a medicine, adds to knowledge about the frequency and severity of these reactions and can help to identify patients who are most at risk.

A privacy notice relating the to the processing of personal data collected by the HPRA in relation to adverse reaction reports is available on the HPRA website

Correspondence/comments should be sent **by email only** to the Pharmacovigilance Section, Health Products Regulatory Authority, medsafety@hpra.ie.

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