Janssen Sciences Ireland UC

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PLEASE READ

IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA An tÚdarás Rialála Táirgí Sláinte Health Products Regulatory Authority

18th October 2022

Topamax: Ongoing EU review of potential risk of neurodevelopmental disorders in children exposed in utero

Dear Healthcare Professional,

Janssen, in agreement with the Health Products Regulatory Authority (HPRA), would like to inform you of the following:

Summary

- The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) is undertaking a review of topiramate and the risk of neurodevelopmental disorders in children exposed to topiramate during pregnancy.
- The review was initiated following the recent publication of findings from a study[1] which suggest a possible increased risk of autism spectrum disorder and intellectual disability in children exposed in-utero to topiramate.
- Use of topiramate in pregnant women is already known to be associated with an increased risk of major congenital malformations (3-fold compared with a reference group not taking antiepileptic drugs) and as well as effects on fetal growth (low birth weight and small for gestational age). For this reason, warnings and precautions for use relating to use of topiramate in women of childbearing potential and in pregnancy are already contained in the product information.
- The PRAC is conducting an in-depth review of the available data on the benefits and risks of topiramate use in pregnant women and women of childbearing potential in the approved indications and will consider if there is a need for any further measures to minimise the risks of topiramate use. The outcome will be communicated when the review is complete.
- Whilst the review is ongoing, topiramate should continue to be used according to the authorised product information. Healthcare professionals should ensure that patients are fully informed of the known and potential risks related to the use of topiramate during pregnancy and the need for highly effective contraception in women of childbearing potential.

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Background on the safety concern

Use of topiramate in pregnant women is already known to increase the risk of major congenital malformations (3-fold compared with a reference group not taking antiepileptic drugs) and fetal growth restriction (low birth weight and small for gestational age).

A study which investigated the risk of neurodevelopmental disorders, including autism spectrum disorder (ASD) and intellectual disability (ID), in association with prenatal exposure to various antiepileptic drugs (AEDs) including topiramate, has been recently published[1]. The study was based on data from several Nordic registries (Denmark, Finland, Iceland, Norway and Sweden), and includes information from more than 24,000 children exposed to at least one AED before birth. Of these children, 471 were exposed to topiramate alone, including 246 children born to mothers who had epilepsy. Prenatal exposure to topiramate was associated with an increased risk of ASD, ID and a combined outcome of any neurodevelopmental disorder. Among unexposed children of mothers with epilepsy, the 8-year cumulative incidence of ASD and ID was 1.5% and 0.8%, respectively, while in children of mothers with epilepsy exposed to topiramate, it was 4.3% and 3.1%. The adjusted hazard ratios for ASD and ID were 2.8 (95%CI, 1.4-5.7) and 3.5 (95%CI, 1.4-8.6), respectively.

The PRAC is conducting an in-depth review of the available data on neurodevelopmental disorders and on the benefits and risks of topiramate in pregnant women and women of childbearing potential in the approved indications and will consider the need for further risk minimisation measures, as appropriate.

Whilst the review is ongoing, topiramate should be used according to the authorised product information as outlined below.

Topiramate – reminder of current warnings and restrictions regarding use in women of childbearing potential and during pregnancy

- **For migraine prophylaxis:** topiramate is contraindicated in pregnancy and in women of childbearing potential if not using a highly effective method of contraception.
- **For epilepsy:** It is recommended to consider alternative therapeutic options in women of childbearing potential. If topiramate is used in women of childbearing potential, advise the use of highly effective contraception. If a woman plans a pregnancy, a preconceptional visit is recommended in order to reassess the treatment, and to consider other therapeutic options. Sudden discontinuation of therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.
- Before the initiation of treatment with topiramate in any woman of childbearing potential, pregnancy testing should be performed, and a highly effective contraceptive method advised. The patient should be fully informed of the risks related to the use of topiramate during pregnancy.

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- The possibility of decreased contraceptive efficacy should be considered in patients taking combination oral contraceptive products with Topamax. Patients taking estrogen containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.
- Refer to the Summary of Product Characteristics (SmPC) for full details of the warnings and restrictions regarding the use of topiramate (Topamax®) in women of childbearing potential and during pregnancy accessible from www.medicines.ie and www.hpra.ie.

Prescribers are reminded:

When prescribing to women of childbearing potential:

- Counsel your patient on the established risks of major congenital malformations, low birth weight and small for gestational age as well as the ongoing review of the available evidence relating to the possible risk of neurodevelopmental effects such as autism spectrum disorders and intellectual disabilities in children exposed to topiramate in the womb.
- Advise the patient to consult their doctor if they wish to become pregnant or immediately if she becomes pregnant so that her treatment can be reassessed.
- Perform a pregnancy test before initiation of treatment.
- Ensure the woman is using highly effective contraception and understands the need to continue use throughout treatment with topiramate. Consider the possibility of reduced effectiveness of combination oral contraceptives.

Pharmacists are reminded:

When dispensing to women of childbearing potential:

- Remind the patient of the risks from use of topiramate in pregnancy and reinforce the need to use effective contraception throughout treatment with topiramate.
- If a woman of childbearing potential reports that she is not using effective contraception, or is planning a pregnancy, or suspects she is pregnant, advise that she contacts her doctor as soon as possible.
- Always provide the patient with a copy of the package leaflet with her medicine. If dispensing outside of original packaging (i.e., broken bulk dispensing or repackaging) cannot be avoided, ensure a copy of the package leaflet is provided to the patient on each occasion that topiramate is dispensed. A copy of the package leaflet is available from www.medicines.ie and www.hpra.ie.

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Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with these products in accordance with the national spontaneous reporting system via HPRA Pharmacovigilance, website www.hpra.ie.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset dates, treatment dates, product brand name and batch numbers.

Suspected adverse reactions should also be reported to Janssen on tel.: 0044(0)1494 567447, fax: +44(0)1494 567799 or by e-mail at dsafety@its.jnj.com.

If you have further questions, please do not hesitate to contact the Janssen Medical Information Department on tel.: 1 800 709122 or email: medinfo@janssen-cilag.co.uk.

Kind regards,

Dr Bríd Seoighe
Head of Medical Affairs
Janssen Ireland

Reference: 1. 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