Direct Healthcare Professional Communication (DHPC) 17 June 2024

Topiramate▼: Introduction of new contraindications and Pregnancy Prevention Programme

Dear Pharmacist,

Janssen Cilag Ltd, in agreement with the other UK marketing authorisation holders of topiramate and the Medicines and Healthcare products Regulatory Agency (MHRA), are contacting you to inform you of the implementation of a Pregnancy Prevention Programme (PPP) for the use of topiramate-containing medicinal products in patients of childbearing potential. This PPP is being implemented following a review of safety data relating to the use of topiramate in pregnancy.

Summary

- A recent review suggests an increased risk of birth defects and low birth weight, and a potential increased risk of autism spectrum disorder, intellectual disability and attention deficit hyperactivity disorder (ADHD) if topiramate is used during pregnancy.
- Because of these increased risks, topiramate should not be used:
    - In pregnancy for prophylaxis of migraine.
    - In pregnancy for epilepsy unless there is no suitable alternative treatment.
- Topiramate should not be used in patients of childbearing potential unless the conditions of the PPP are fulfilled.
- The PPP aims to ensure that for patients who are able to get pregnant:
    - Pregnancy is excluded before starting topiramate.
    - They are aware of the risks of topiramate use during pregnancy and the need to adhere to the PPP.
    - They understand the need to use highly effective contraception throughout treatment with topiramate and for at least 4 weeks after the last dose of topiramate.
    - Topiramate treatment is subject to regular, at least annual, review.

Actions for Pharmacists

- Ensure the Patient Card is provided every time topiramate is dispensed.
- Remind patients of:
    - The risks in pregnancy.
    - The need to use highly effective contraception throughout treatment with topiramate.
    - The need for annual review.
- If a patient of childbearing potential is not aware of the need for contraception and has not been seen by their GP in the past year, dispense their medicine and refer them to their GP (including by contacting the GP if necessary).

In patients of childbearing potential[1]

Topiramate for migraine prophylaxis is contraindicated:

- In pregnancy.
- In patients of childbearing potential unless the conditions of the PPP are fulfilled.

Topiramate for epilepsy is contraindicated:

- In pregnancy unless there is no suitable alternative treatment.
- In patients of childbearing potential unless the conditions of the PPP are fulfilled.

The patient must be fully informed and understand the risks related to the use of topiramate during pregnancy. This includes the need to consult their doctor as soon as they are planning for pregnancy, and for prompt contact with their doctor-if they become pregnant or think they may be pregnant and are taking topiramate.

Contraception

Patients 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 and for at least 4 weeks after stopping treatment.

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

Further information on the potential for drug interactions with hormonal contraceptives is provided in the 'Faculty of family planning and sexual health' guidance[7].

Patient advice regarding pregnancy

Any patient who is planning to have a baby should be advised to make an appointment with their GP. They should not stop using topiramate and contraception before they have talked to their doctor.

If a patient who is taking topiramate for epilepsy is pregnant or thinks they might be pregnant, they should be advised to make an urgent appointment with their GP or epilepsy team. They should not stop taking topiramate, as this may cause their seizures to start again or happen more often and last longer.

If a patient who is taking topiramate for migraine prevention is pregnant or thinks they might be pregnant, they should stop taking topiramate straight away and contact their GP.

Educational materials

Educational materials have been created to support healthcare professionals and patients. Please find the following materials attached to this letter:

- 3 copies of patient guides (separate guides are provided for Epilepsy and for Prophylaxis of migraine)
- 20 copies of patient card
  These copies are to be given to female patients/patients of childbearing potential. At a later date the patient card will be included in the box of the medicine or attached to the carton once updated packaging is implemented.
- 1 copy of healthcare professional guides (separate guides are provided for Epilepsy and for Prophylaxis of migraine)

Annual Risk Awareness Forms have also been produced. These have been sent to prescribers only.

These new materials are available in electronic form and for printing at https://www.medicines.org.uk or at the appropriate company website.

Call for Reporting

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme.

Topiramate ▼ is subject to additional monitoring. This will allow quick identification of new safety information.

Please report:

- all suspected adverse drug reactions (ADRs) to drugs and vaccines identified by the black triangle▼ to the MHRA through the Yellow Card scheme.
- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.

You can report via:

- The Yellow Card website - https://yellowcard.mhra.gov.uk/
- The free Yellow Card app available from the Apple App Store or Google Play Store.
- Some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals.

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm.

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

Adverse events should also be reported to the Marketing Authorisation Holder, using the contact details provided below.

Company Contact Point

If you have further questions regarding the use of topiramate, please do not hesitate to contact the manufacturer, using the contact details provided in the table below.

Yours sincerely,

John Fleming MRCP

Country Medical Director

Janssen-Cilag Limited

This letter is sent on behalf of the Marketing Authorisation Holders of the topiramate-containing medicines.

Changes to the product information

The product information (Summary of Product Characteristics and Patient Information Leaflet) is being updated to reflect the new safety information. At a later date, a warning will be also placed on the outer packaging of the medicine. As an interim solution, warning stickers are available on eMC (https://www.medicines.org.uk) for printing and to be included on the outer packaging until new packaging is implemented.

Background on the safety concern

Topiramate is licensed[1] for:

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.

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. Topiramate is not intended for acute treatment.

The Commission on Human Medicines (CHM) conducted a Major Safety Review to explore the increased risk of neurodevelopmental disabilities in children with prenatal exposure. The review considered the available data and concluded the following:

Congenital malformations:

In a study in the North American Antiepileptic Drug pregnancy registry, around 4.3% of children exposed to topiramate monotherapy had a major congenital malformation vs 1.4% not exposed to antiseizure medication[2]. A further study showed a 2 to 3-fold higher prevalence of major congenital malformations in topiramate exposed children (up to 9.5%) compared with children not exposed to antiseizure medication[3] (3.0%).
The risk of congenital malformations with topiramate appears to be dose dependent, however, adverse effects are observed at all doses.

Developmental disorders:

Two observational studies[4,5] suggest there may be a 2- 3 fold higher prevalence of autism spectrum disorders, intellectual disability or ADHD in children of mothers with epilepsy exposed to topiramate in utero vs those not exposed to antiseizure medication.
A third study[6] did not suggest an increased cumulative incidence of these outcomes by 8 years of age in children of mothers with epilepsy exposed to topiramate in utero vs those not exposed to antiseizure medication.

Fetal growth restriction:

A higher prevalence of low birth weight and small for gestational age (SGA) (birth weight corrected for gestational age and sex) was found in topiramate exposed children compared with a reference group.
The risk of SGA in children of women receiving topiramate was 18% vs 5% for children of women not taking antiseizure medication[2].

Marketing Authorisation Holder	Email	Phone
Janssen-Cilag Ltd.	dsafety@its.jnj.com medinfo@its.jnj.com	+44 (0)1494 567447 +44 (0)800 731 8450
Morningside Healthcare Limited	medicalenquiry@Morningsidehealthcare.com	+44 (0)345 4592137
Cadila Pharmaceuticals (UK) Ltd.	safety.uk@lambda-cro.com	00 800 890 13370
Torrent Pharma UK Ltd	Medinfo.Torrent@apcerls.com	0800 0885366
Mylan (A Viatris Company)	Medical Enquiries: info.uk@viatris.com Adverse Events: pv.uk@viatris.com	Medical Enquiries: 01707 853 000 (option 1) Adverse Events: 01707 853 000 (option 5)
Renata (UK) Limited	drugsafetyrenata@mitoconbiopharma.com	+1 732-250-0025
Crescent Pharma Limited	safety@crescentpharma.com	+44 1217901596
Rosemont Pharmaceuticals Ltd	pharmacovigilance@rosemontpharma.com	+44 (0)113 244 1400
Accord Healthcare Ltd, Accord-UK Ltd	medinfo@accord-healthcare.com	+44 (0)1271 385487
Milpharm Limited	MEDINFO@aurobindo.com	0208 845 8811 (Option 1)
Glenmark Pharmaceuticals Europe Ltd	Medical_information@glenmarkpharma.com	0800 458 0383
Zydus Pharmaceuticals UK Limited	DrugSafety@ZydusUK.com	(0800) 9956034

1. EMC Topiramate page https://www.medicines.org.uk/emc/search?q=Topiramate
2. North American Antiepileptic Drug Pregnancy Registry https://www.aedpregnancyregistry.org/
3. Cohen JM, Alvestad S, Cesta CE, et al. Comparative Safety of Antiseizure Medication Monotherapy for Major Malformations. Ann Neurol. 2023; 93(3):551-562
4. 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.
5. 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.
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.
7. Faculty of Sexual and Reproductive Healthcare. Clinical Guidance: drug interactions with hormonal contraception, May 2022 update. FSRH Drug Interactions