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Department of Health
An Roinn Sláinte
Männystrie O Poustie
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HSS(MD) 21/2024

FOR ACTION
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Deputy Secretary SPPG
GP Medical Advisers, SPPG
All General Practitioners and GP Locums (for onward distribution to practice staff) and Community Pharmacies
OOHs Medical Managers (for onward distribution to staff)

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Dear Colleague

MHRA DRUG SAFETY UPDATE – TOPIRAMATE (TOPAMAX): INTRODUCTION OF NEW SAFETY MEASURES, INCLUDING A PREGNANCY PREVENTION PROGRAMME

The Medicines and Healthcare products Regulatory Agency (MHRA) have issued a Drug Safety Update, available at the following link.

Topiramate is now contraindicated in pregnancy and in women of childbearing potential unless the conditions of a Pregnancy Prevention Programme are fulfilled.

This follows a review by the MHRA which concluded that the use of topiramate during pregnancy is associated with significant harm to the unborn child. Harms included a higher risk of congenital malformation, low birth weight and a potential increased risk of intellectual disability, autistic spectrum disorder and attention deficit hyperactivity disorder in children of mothers taking topiramate during pregnancy.

The Department is liaising with SPPG colleagues and the PHA to ensure the appropriate co-ordination, reporting and oversight arrangements are in place regarding implementation. All healthcare professionals involved in the prescribing or supply of topirmate should be aware of the new regulatory requirements and take action to implement these with immediate effect.

General advice for healthcare professionals:

- topiramate should not be used:
    - in pregnancy for prophylaxis of migraine
    - in pregnancy for epilepsy unless there is no other suitable treatment
- topiramate should not be used in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled. This aims to ensure that all women of childbearing potential:
    - are using highly effective contraception
    - have a pregnancy test to exclude pregnancy before starting topiramate
    - are aware of the risks from use of topiramate
- please see specific advice for prescribers and advice for dispensers
- ensure women of childbearing potential sign the Risk Awareness Form, you will receive materials including the Risk Awareness Form by post in the coming weeks to use in the implementation of the Pregnancy Prevention Programme
- report suspected adverse drug reactions associated with topiramate to the Yellow Card scheme

Advice for healthcare professionals to provide to patients:

- new measures are being introduced because there is evidence that taking topiramate during pregnancy can increase the risk to the baby of congenital malformation, low birth weight, intellectual disability, autistic spectrum disorder and attention deficit hyperactivity disorder
- use effective birth control (contraception) at all times during your treatment with topiramate and for at least 4 weeks after the last dose
- topiramate may interact with some hormonal contraceptives. Your General Practitioner (GP), specialist, sexual health and contraception clinic or contraception service in community pharmacy will discuss which method of birth control is best for you
- if you are thinking about having a baby, make an appointment with your GP. Do not stop using topiramate and contraception before you have talked to your doctor
- if you think you are pregnant and are taking topiramate for epilepsy, do not stop using topiramate. This may cause your seizures to start again or happen more often and last longer. Make an urgent appointment with your GP or epilepsy team (within a few days)

Advice for healthcare professionals to provide to patients: (continued)

- if you think you are pregnant and are taking topiramate for migraine prevention, stop taking topiramate straight away and contact your GP
- it is important to visit your doctor to review your treatment at least once each year
- always read the safety leaflet that comes with your medicine and consult the new Patient Guide for information about the risk of topiramate use during pregnancy

Review of harms of topiramate use during pregnancy

Topiramate is indicated for the prophylaxis of migraine and for the treatment of epilepsy. It is available as tablets, a liquid oral solution and as capsules that can be swallowed whole or sprinkled on soft food. The brand name of topiramate is Topamax, and so this may also appear on the box. Topiramate has been contraindicated in pregnancy for the prophylaxis of migraine since 2010.

Following a comprehensive review of the safety of antiseizure medications in pregnancy, including topiramate, new safety advice was published in January 2021. Since then, new study data has become available reporting a potential increased risk of autism spectrum disorder and effects on learning development in children exposed to topiramate during pregnancy[1]. These new data, and data suggesting increasing use of topiramate in women of childbearing age, triggered a new safety review. This review examined the available data on the risk of congenital malformations, effects on growth and development of the baby, and the risk of neurodevelopmental disorders when topiramate is used during pregnancy.

The review concluded that the use of topiramate during pregnancy is associated with significant harm to the unborn child (both from the confirmed risks of congenital malformations and low birth weight and the potential risk of neurodevelopmental disorders). The accumulating data suggest that:

- topiramate is amongst the antiseizure medications associated with a higher risk of congenital malformations (approximately 4 to 9 per 100 babies compared to around 1 to 3 babies in every 100 in the general population)[2]

- the risk of congenital malformations with topiramate appears to be dose-dependent, however, a threshold dose below which no risk exists cannot be established

[1] Bjørk MH and others. Association of Prenatal Exposure to Antiseizure Medication with Risk of Autism and Intellectual Disability. JAMA Neurology 2022: volume 79, pages 672 to 681
[2] Cohen JM and others. Comparative Safety of Antiseizure Medication Monotherapy for Major Malformations. Annals of Neurology 2023: volume 93, pages 551 to 562

- topiramate is associated with a high prevalence of babies being born small for gestational age and weighing less at birth (approximately 18 per 100 babies affected); this is higher than the risk in babies born to women with epilepsy not taking antiseizure medication (approximately 5 in 100 babies affected) and may be higher than the risk with some other antiseizure medications[3]

- topiramate may be associated with an approximately 2 to 3 times increased risk of intellectual disability, autistic spectrum disorders and attention deficit hyperactivity disorder compared with children born to mothers with epilepsy not taking antiseizure medication.[1] [4] [5] [6] [7] [8]

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Full information on the studies considered and the findings, can be found in the Public Assessment Report. This report also includes a plain language summary of the review and findings.

New safety measures

Due to the accumulating data on these harms, further restrictions are being introduced with regards to the use of topiramate in women of childbearing potential and in pregnancy.

The use of topiramate is now contraindicated:

- in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (for all indications)
- in pregnancy for prophylaxis of migraine
- in pregnancy for epilepsy unless there is no other suitable treatment

Materials to support the Pregnancy Prevention Programme:

Healthcare professionals will receive materials by post in the coming weeks to support discussions with patients and implementation of the Pregnancy Prevention Programme. These materials are also available online and consist of :

[3] Hernandez-Diaz S and others. Fetal growth and premature delivery in pregnant women on anti-epileptic drugs. Annals of Neurology 2017: volume 82, pages 457to 465
[4] Blotière PO and others. Risk of early neurodevelopmental outcomes associated with prenatal exposure to the antiepileptic drugs most commonly used during pregnancy: a French nationwide population-based cohort study. BMJ Open 2020: volume 10, page e034829.
[5] Bromley RL and others. Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate. Neurology 2016: volume 87, pages 1943 to 1953
[6] Dreier JW and others. Prenatal Exposure to Antiseizure Medication and Incidence of Childhood- and Adolescence-Onset Psychiatric Disorders. JAMA Neurology 2023: volume 80, pages 568 to 577.
[7] Hernandez-Diaz S and others. Topiramate during pregnancy and the risk of neurodevelopmental disorders in children. Pharmacoepidemiology and Drug Safety 2022: volume 31, page 11. [Full study unavailable at time of review]
[8] Knight R and others. Adaptive behaviour in children exposed to topiramate in the womb. A thesis submitted to the University of Manchester for the degree of Doctor of Clinical Psychology in the Faculty of Biology, Medicine, and Health. 2020

Patient Guide for Migraine and Epilepsy - to be provided to all girls and women of childbearing potential who are started on, or continue to use, topiramate-containing medicines

Guide for Healthcare Professionals for Migraine and Epilepsy
Risk Awareness Form for Migraine and Epilepsy - for the healthcare professional and the patient (or responsible person) to sign at initiation of treatment with topiramate and at annual treatment reviews. The patient should receive a copy of this form, a copy should be filed in the patient's medical notes, and, if necessary, a copy sent to the patient's GP

Patient Card - to be given by pharmacists to all female patients who are dispensed topiramate to inform them of the risks

See advice for prescribers and advice for dispensers overleaf.

Advice for prescribers:

- all women of childbearing potential being treated with topiramate-containing medicines must follow the requirements of the Pregnancy Prevention Programme. These conditions are also applicable to female patients who are not sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy

- for all new women of childbearing, potential prescribers must:
    1. assess their potential for pregnancy and discuss the need for them to be on the Pregnancy Prevention Programme
    2. ensure that pregnancy has been excluded, by means of a negative pregnancy test, prior to starting treatment with topiramate
    3. inform them of the potential risks of topiramate use in pregnancy and counsel them on treatment options
    4. discuss with them the need to use highly effective contraception throughout treatment and for at least four weeks after the last dose of topiramate. See guidance from Faculty of Family Planning and Sexual Health on potential drug interactions with hormonal contraceptives and what this means for topiramate
    5. complete the Risk Awareness Form with the patient (or responsible person)
    6. provide a copy of the Patient Guide to the patient (or responsible person)

- for existing patients, prescribers must:
    1. identify all women and girls of childbearing potential on topiramate and invite them in for review
    2. complete the Risk Awareness Form with the patient (or responsible person) and at each annual review
    3. provide a copy of the Patient Guide to the patient (or responsible person)

Advice for dispensers:

- a visual warning symbol will be added to the pack of topiramate. This symbol will show a pregnant woman in a red circle with a line through it, with warning text about the risks and information about the new measures
- until warning symbols are present on packs, stickers will be available to print locally on eMC
- pharmacists should dispense in whole packs whenever possible. This will ensure that patients always see the warning symbol and receive the statutory information
- pharmacists should give the patient card to female patients when dispensing topiramate
- ask women or girls of childbearing potential if they are taking highly effective contraception, if they are not, pharmacists should advise them to contact their GP for a follow-up appointment

Report suspected reactions on a Yellow Card

Please continue to report suspected adverse drug reactions to the Yellow Card scheme.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals

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

The MHRA Drug Safety Update is available at the following link.

Thank you for your support in implementing these new safety measures

Yours sincerely

Professor Sir Michael McBride
Chief Medical Officer

Professor Cathy Harrison
Chief Pharmaceutical Officer

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