Medicines & Healthcare products Regulatory Agency

Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

Volume 17 Issue 11 June 2024

Contents

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

NICE accredited
www.nice.org.uk/accreditation

NICE has accredited the process used by the MHRA to produce Drug Safety Update guidance. More information on accreditation can be viewed on the NICE website.

To subscribe to monthly email alerts of Drug Safety Update see: https://www.gov.uk/drug-safety-update

In our first article, we advise that topiramate (Topamax) is contraindicated in pregnancy and women of childbearing potential unless the conditions of a Pregnancy Prevention Programme are fulfilled. This follows the conclusion of a major safety review by the MHRA which found use of topiramate during pregnancy is associated with significant harm to the unborn child.

Secondly, we remind healthcare professionals to be alert to the risk of harmful drug interactions between warfarin and tramadol. Healthcare professionals should ask patients which medications they are currently taking and ensure patients are aware of the need to seek medical advice should they notice signs of a major bleeding event.

Finally, we provide a summary of recent letters and notifications sent to healthcare professionals about medicines.

If you have been forwarded this issue of Drug Safety Update, subscribe directly via our website.

Topiramate (Topamax): introduction of new safety measures, including a Pregnancy Prevention Programme

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.

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)

- 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
- 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]

Full information on the studies considered and their 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:

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

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 (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

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

Article citation: Drug Safety Update volume 17, issue 11: June 2024: 1

References

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.
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.

Warfarin: be alert to the risk of drug interactions with tramadol

Taking warfarin and tramadol together can cause harmful drug interactions, which can raise the International Normalised Ratio (INR), and result in severe bruising and bleeding, which in some patients could be fatal.

Advice for healthcare professionals:

- warfarin is a coumarin-derived vitamin K antagonist which has a low therapeutic index, so continue to exercise caution when co-prescribing warfarin with other drugs, to minimise the risk of drug interactions
- ask patients about all the medicines that they are currently taking
- be aware of the risk of increased INR when warfarin and tramadol are used together, with a risk of major bruising and bleeding which could be life-threatening
- consult the product information of any new concomitant therapy for specific guidance on use with warfarin and consider whether warfarin dose adjustment is required
- consider whether additional monitoring of INR is required when starting tramadol or another concomitant medicine
- ensure patients are aware of the need to seek medical treatment should they notice the signs of a major bleeding event
- caution should also be taken if tramadol is co-prescribed with other coumarin-derived anticoagulants such as acenocoumarol
- report suspected adverse drug reactions to the Yellow Card scheme

Advice for healthcare professionals to provide to patients:

- warfarin can interact with some medicines, such as tramadol, leading to an increased risk of bleeding
- you should seek medical treatment and have an urgent International Normalised Ratio test should you experience any of the following symptoms:
    - prolonged nose bleeds (more than 10 minutes)
    - blood in vomit, sputum (phlegm), stool (poo) or urine (pee)
    - severe or unexplained bruising
    - severe bleeding gums
    - unusual headaches (headaches with blurred vision, slurred speech, loss of movement, feeling or being sick, fits, loss of consciousness, dizziness)
    - women who experience heavy or increased bleeding during their menstrual period or any other heavy vaginal bleeding
- inform your healthcare professional that you are taking warfarin and carry your anticoagulant alert card with you at all times
- inform your healthcare professional of all the medicines you are currently taking
- do not take any new medicines without first discussing this with your healthcare professional
- do not stop taking warfarin without first discussing this with your healthcare professional
- report suspected adverse drug reactions to the Yellow Card scheme

Risk of adverse drug interaction with tramadol

The MHRA has received a Coroner's report following the death of a patient who died from a bleed on the brain, following concurrent treatment with warfarin and tramadol. Taking warfarin and tramadol together may increase a patient's INR and increase the risk of bleeding. The Coroner raised concerns that the interaction between warfarin and tramadol was not well known and emphasised the need to highlight this interaction to healthcare professionals.

Warfarin is a coumarin-derived vitamin K antagonist used for prevention and treatment of blood clots. It is used to prevent embolisation in rheumatic heart disease and, atrial fibrillation and after insertion of prosthetic heart valves. Warfarin is also used in the prevention and treatment of venous thrombosis and pulmonary embolism and treatment of transient ischaemic attacks.

Warfarin has a low therapeutic index, which means care is required when taking co-prescribed medicines due to the possibility of interactions that could lead to an increased risk of bleeding.

The product information for warfarin advises that healthcare professionals should refer to the product information of any new concomitant medicines for specific guidance on use with warfarin and whether a dose adjustment or therapeutic monitoring is required. The product information will be updated to include the interaction in due course.

Tramadol is a non-selective opioid analgesic, which acts as an agonist at the mu, delta and kappa opioid receptors. Section 4.5 of the tramadol Summary of Product Characteristics (SmPC) states that caution should be exercised during concomitant treatment with coumarin derivatives such as warfarin due to reports of increased INR with major bleeding and bruising in some patients. While the risk of major bleeding with warfarin treatment is rare, the risk may be increased with concurrent use of tramadol.

Report any suspected adverse drug reactions

Please continue to report suspected adverse drug reactions (ADRs) to the Yellow Card scheme. Reporting suspected ADRs, even those known to occur, adds to knowledge about the frequency and severity of these reactions and can be used to identify patients who are most at risk. Your report helps the safer use of medicines.

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 (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

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

Article citation: Drug Safety Update volume 17, issue 11: June 2024: 2

Letters and medicine recalls sent to healthcare professionals in May 2024

A summary of recent letters and notifications sent to healthcare professionals about medicines and medical devices.

Letters

In May 2024, the following letters were sent or provided to relevant healthcare professionals:

- Sodiofolin® (folinic acid) 50mg/ml solution for injection/infusion, strengths 100mg and 400mg, PL 11587/0005 – requirement to use a PES or PVDF filter due to observation of particles and potential risk of thrombo-embolic event

Medicine Recalls and Notifications

In May 2024, recalls and notifications for medicines were issued on:

Class 4 Medicines Defect Information: Cygnus Pharma Ltd, Trazodone Hydrochloride 50mg/5ml Oral Solution, EL (24)A/16. Issued: 20 May 2024. Cygnus Pharma Ltd. have informed the MHRA that the European Article Number (EAN) barcode printed on various packs of Trazodone Hydrochloride 50mg/5ml Oral Solution is defective and returns the incorrect information.

Class 3 Medicines Defect Information: Doncaster Pharma Limited, Keppra 500mg film-coated tablets, EL(24)A/15. Issued: 22 May 2024. The MHRA has re-issued this notification as a Class 3 recall based on further assessment. Please note the new actions for healthcare professionals listed within the notification. Doncaster Pharma Limited have identified an error relating to the Braille printed on the cartons on various parallel imported packs which have been repackaged by BModesto B.V.

Class 4 Medicines Defect Information: Fresenius Kabi Limited, Sodium Chloride 0.9% Intravenous Infusion BP (Freeflex and Freeflex Plus), EL (24)A/17. Issued: 22 May 2024. Fresenius Kabi Limited have informed the MHRA of a packaging error with specific batches of Sodium Chloride Intravenous Infusion 0.9% Freeflex and Freeflex PLUS. Some batches were packaged without the patient information leaflet (PIL), and some were packaged with an older version of the PIL.

Article citation: Drug Safety Update volume 17, issue 11: June 2024: 3