Medicines & Healthcare product 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

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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.

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This month we inform of the start of a new safety review into topiramate, triggered by a recently published observational study reporting an increased risk of neurodevelopmental disabilities in children with prenatal exposure. While the review is ongoing, we alert healthcare professionals to the findings of this new study and remind of the important precautions to take when prescribing or dispensing topiramate for migraine prevention and epilepsy.

On page 8, we summarise recent advice relating to COVID-19 vaccines and medicines published since the June 2022 issue of Drug Safety Update. And on page 9, we include recent letters, recalls, and notifications sent to healthcare professionals about medicines and medical devices.

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Topiramate (Topamax): start of safety review triggered by a study reporting an increased risk of neurodevelopmental disabilities in children with prenatal exposure

We have initiated a new safety review into topiramate as a result of an observational study reporting an increased risk of neurodevelopmental disabilities in children whose mothers took topiramate during pregnancy.

Topiramate is known to be associated with an increased risk of congenital malformations and effects on fetal growth if used during pregnancy. Continue to counsel patients who can become pregnant on the known and emerging risks of topiramate for an unborn baby and on the need to use effective contraception throughout use.

Advice for healthcare professionals:

- we have started a new safety review to assess the benefits and risks of topiramate and to consider whether further measures are required to reduce the risk of harm associated with topiramate use during pregnancy
- the new safety review was triggered by a large observational study reporting that prenatal exposure to topiramate is associated with an increased risk of autism spectrum disorders, intellectual disability, and neurodevelopmental disorders
- of the antiepileptic medicines reviewed for use in pregnancy, lamotrigine and levetiracetam continue to be considered the safer for the baby since they were not associated with an increased risk of birth defects – see advice following comprehensive safety review of antiepileptic drugs in pregnancy
- it remains vital that the strict restrictions for valproate prescribing in women and girls of childbearing potential are followed given the known significant risks if valproate is used in pregnancy (see dedicated section on page 5)

Reminder of current advice for topiramate:

- do not prescribe topiramate during pregnancy for migraine prophylaxis
- ensure any patients of childbearing potential know to use highly effective contraception throughout treatment with topiramate
- counsel patients on the importance of avoiding pregnancy during topiramate use due to these emerging data and also the established increased risks of major congenital malformations and fetal growth restriction in babies exposed to topiramate in-utero
- topiramate may reduce the effectiveness of steroidal contraceptives, including oral contraceptives, therefore consider alternative or concomitant methods (see section on Advice on contraceptive interactions in the article)
- for migraine prophylaxis, topiramate can be withdrawn in pregnancy by an appropriate prescriber but alternative treatments should be considered
- for epilepsy, urgently refer anyone on topiramate who is planning a pregnancy or who is pregnant for specialist advice on their antiepileptic treatment

Advice to provide to patients:

- do not stop taking topiramate without first discussing it with your doctor
- topiramate can harm the way an unborn baby grows and develops during pregnancy – see advice on epilepsy medicines and pregnancy
- a new study has also linked topiramate to an increased risk of autism spectrum disorders and intellectual disabilities (effects on learning and development) in children exposed to it during pregnancy
- the MHRA and its independent experts are investigating whether there needs to be changes to how topiramate can be used in UK patients – we will communicate the outcomes of this review once it has concluded
- if you are taking topiramate for epilepsy and are planning a pregnancy, urgently talk to your doctor for a specialist review – there are other epilepsy medicines that are not associated with an increased risk of birth defects in pregnancy
- if you are taking topiramate for migraine and planning a pregnancy, talk to your prescriber about alternative treatments that can be used in pregnancy as soon as possible
- anyone who is able to get pregnant should have a pregnancy test before they start topiramate treatment and use effective contraception while taking topiramate
- topiramate can reduce the effectiveness of hormonal contraception in preventing unplanned pregnancy – talk to a healthcare professional about the best contraception for you while you are taking topiramate

Topiramate and known harms if used in pregnancy

Topiramate is used:

- to prevent migraine headaches in adults after consideration of possible alternative treatment options
- alone to treat seizures in adults and children aged older than 6 years
- with other medicines to treat seizures in adults and children aged 2 years and older

It is available as tablets, a liquid oral solution, or 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.

Following a comprehensive national review by the Commission on Human Medicines into the safety of antiepileptic drugs in pregnancy, including topiramate, in January 2021 we published new safety advice in Drug Safety Update with patient advice, and a Public Assessment Report.

The review showed topiramate exposure in-utero to be associated with an increased risk of congenital malformations (approximately 4 or 5 cases per 100 babies, compared with 2 or 3 in the general population). Topiramate was also shown to be associated with an increased risk of the baby being born of low birth weight and small for gestational age (fetal growth restriction).

At the time of the 2021 review, some data had raised concerns that topiramate use during pregnancy may be associated with an increased risk of autism spectrum disorder and poorer developmental outcomes. However, the numbers in the available studies were limited and further data were needed to reach firm conclusions.

Clinicians should continue to consult the wider findings of the review when considering prescribing of epilepsy medicines in female patients, particularly that lamotrigine (Lamictal) and levetiracetam (Keppra) were not associated with an increased risk of birth defects compared with the general population.

New national safety review of topiramate

The MHRA regularly reviews any emerging data relating to the safety of topiramate, as for all medicines. A recently published study (Bjørk and colleagues[1]) reported prenatal exposure to topiramate to be associated with an increased risk of autism and intellectual disability. The Commission on Human Medicines considered the findings of this new study and advised that it provides robust evidence to support an association between prenatal exposure to topiramate and an increased risk of autism spectrum disorder, intellectual disability and the composite outcome of any neurodevelopmental disorder (see study for definition).

We have now started a safety review to evaluate these findings in the context of the accumulating data relating to the benefits and risks of use of topiramate, with a particular focus on women of childbearing potential and during pregnancy. The review will also explore the need for additional risk minimisation measures to reduce the potential harms associated with the use of topiramate during pregnancy. More about the review is available on our website.

While the review is ongoing, we are alerting healthcare professionals to the findings of this new study and reminding you of the important risks and precautions to take when prescribing or dispensing topiramate in women of childbearing potential.

Further details on the findings of the new study

The study by Bjørk and colleagues[1] is a large, well-conducted study using established data sources from 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). It reports that children whose mothers use topiramate or valproate during pregnancy are at an increased risk of autism spectrum disorder, intellectual disability, and a composite outcome of any neurodevelopmental disorder. These risks are known for valproate (see section on valproate on page 5).

Data from around 4.5 million mother-child pairs were examined and this included 24,825 children (0.6%) who were prenatally exposed to antiepileptic drugs. Of these, 16,170 were born to mothers who had epilepsy. These data were analysed to estimate the risk of autism spectrum disorder and intellectual disability after exposure to the 10 most frequently used antiepileptic drugs when used as monotherapy (one medicine) and the 5 most frequently used antiepileptic drugs when used as duotherapy (two medicines at the same time).

In unexposed children of mothers with epilepsy, the 8-year cumulative incidence of autism spectrum disorder and intellectual disability were 1.5% and 0.8% respectively compared with 4.3% and 3.1% in children of mothers with epilepsy exposed to topiramate. The adjusted hazard ratios for autism spectrum disorder and intellectual disability were 2.8 (95% CI 1.4 to 5.7) and 3.5 (95% CI 1.4 to 8.6).

A range of sensitivity analyses were conducted that broadly showed consistent and statistically significant effect estimates of a greater than 2-fold increase in risk of neurodevelopmental disorders across most of the analyses. The data also showed a dose-dependent effect for topiramate.

Topiramate and current pregnancy prevention requirements

Before the initiation of topiramate in a woman of childbearing potential, pregnancy testing should be performed, and the patient should be fully informed of the risks if used during pregnancy.

For epilepsy, alternative therapeutic options should be considered for women of childbearing potential. If topiramate is used, a highly effective contraception is strongly recommended, and the discussion with the patient should include information on both the risks associated with taking topiramate and of uncontrolled epilepsy 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. As such, topiramate should not be prescribed for migraine prevention in a patient who is pregnant.

Advice on contraceptive interactions

Topiramate may reduce the effectiveness of steroidal contraceptives, including oral contraceptives. Alternative or concomitant methods of contraception should be considered. Consult clinical guidance, including that from the Faculty of Reproductive and Sexual Health Clinical Effectiveness Unit (May 2022).

When using any medicine with teratogenic potential, the most effective contraceptive method should be advised, taking into account their personal circumstances.

Valproate: current strict restrictions

Valproate (Epilim) is highly teratogenic and evidence supports a rate of congenital malformations of 10% in infants whose mothers took valproate during pregnancy and neurodevelopmental disabilities in approximately 30% to 40% of children. The available data show these risks are dose-dependent, however there is no safe dose of valproate that can be used in pregnancy.

Valproate should not be used in girls and women of childbearing potential unless other treatments are ineffective or not tolerated, as judged by an experienced specialist. Valproate is contraindicated in women of childbearing potential unless a pregnancy prevention programme is in place.

All healthcare professionals must continue to identify and review all female patients of childbearing potential on valproate, including when it is used outside the licensed indications. Specialists should discuss the risks and review their treatment according to their clinical condition and circumstances. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued.

The comprehensive safety review of antiepileptic drugs in pregnancy in 2021 showed that available information for lamotrigine (brand name Lamictal) and levetiracetam (brand name Keppra) does not suggest an increased risk of physical birth defects compared with the general population.

The MHRA continues to closely monitor the use of valproate in female patients in the UK and is considering the effectiveness of the current measures to support its safe use.

Medicines and Pregnancy Registry

Healthcare professionals should continue to use the data provided by the Medicines and Pregnancy Registry - Antiepileptic use in females aged 0 to 54 in England to review comparative use of antiepileptic medicines in pregnancy.

The MHRA and NHS Digital are working together on the Medicines in Pregnancy Registry, which is built around a core register of routinely collected prescribing data for all women in England who are taking NHS-prescribed antiepileptic medications regardless of the indication for use.

The report from the registry was updated on 31 March 2022 to include data up to September 2021. An interactive dashboard is available to review the data and how prescribing of antiepileptic medicines in pregnancy has changed over time.

The latest data show that while prescribing of valproate has declined substantially in girls and women of childbearing age, as well as during pregnancy, a number of pregnancies continue to be exposed. Conversely, total prescribing of topiramate across indications is increasing, and it is now one of the more commonly prescribed antiepileptics in women younger than 55 years of age, including during pregnancy.

Report suspected reactions on a Yellow Card

Please continue to report any suspected adverse drug reactions (ADRs) associated with topiramate or any other medicines via the Yellow Card scheme.

All patients, caregivers, and healthcare professionals can report a Yellow Card when they suspect a medication used during pregnancy has caused an adverse reaction or adverse pregnancy outcome.

When reporting ADRs related to medicines used in pregnancy, information that is particularly valuable for our assessment of the report includes:

- timings of when the medicine was taken during the pregnancy
- the outcome of the pregnancy (when known)
- details of any relevant family history, including any obstetric history
- for reports concerning congenital malformations, a detailed clinical description of any congenital anomaly and the results of any imaging (for example, scans), or laboratory tests
- other relevant information, including other medications or substances taken during the pregnancy, as well as folic acid intake.

Report Yellow Cards 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)

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Footnotes

1. Bjørk MH and others. Association of Prenatal Exposure to Antiseizure Medication with Risk of Autism and Intellectual Disability. *JAMA Neurology:* published 31 May 2022.

COVID-19 vaccines and medicines: updates for July 2022

Recent information relating to COVID-19 vaccines and medicines that has been published since the June 2022 issue of Drug Safety Update, up to 20 July 2022.

Product information updates for Vaxzevria

We have recently updated the product information for Vaxzevria (COVID-19 Vaccine AstraZeneca). These changes included updating preclinical data for breastfeeding and updating the efficacy, safety and immunogenicity data. Wording has also been updated to state that in clinical trials, transient mild thrombocytopenia was commonly reported.

For more information about Vaxzevria, please see the Decision page with the Summary of Product Characteristics and Patient Information Leaflet.

Summaries of Yellow Card reporting – update to publication frequency

We continue to publish the summaries of the Yellow Card reporting for the COVID-19 vaccines being used in the UK. The report summarises information received via the Yellow Card scheme and includes other data such as usage of COVID-19 vaccines and relevant epidemiological data. The report is updated regularly to include other safety investigations carried out by the MHRA under the COVID-19 Vaccine Surveillance Strategy.

In line with the wider government's Living with COVID-19 agenda strategy, the frequency of publication of the updated summary has changed to every other week, before transitioning to once per month from August. Our robust safety monitoring and surveillance will continue in the normal way between publications and we will continue to communicate promptly on any updated safety information.

See guidance on COVID-19 for all our latest information, including after publication of this article. We previously included summaries of latest COVID-19 information, including in the April 2022, May 2022 and June 2022 issues of Drug Safety Update.

Reporting Yellow Cards

Report suspected side effects to medicines, vaccines, medical device and test kit incidents used in coronavirus (COVID-19) testing and treatment using the dedicated Coronavirus Yellow Card reporting site or via the Yellow Card app.

As these products are under additional monitoring, this includes all suspected adverse reactions associated with these vaccines. This will allow quick identification of new safety information. When reporting please provide as much information as possible, including information about medical history, any concomitant medications, onset, treatment dates, and vaccine product brand name and batch number.

You may be contacted following submission of a Yellow Card report so that we can gather additional relevant information for the assessment of the report. These contributions form an important part of our understanding of suspected adverse events.

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Letters and medicine recalls sent to healthcare professionals in June 2022

Letters

In June 2022, the following letters were sent or provided to relevant healthcare professionals:

- Dexmedetomidine: clinical trial finds increased risk of mortality in intensive care unit (ICU) patients aged 65 years or younger
- Defitelio (defibrotide): Do not use for prophylaxis of veno-occlusive disease (VOD) after post-hematopoietic stem-cell transplantation (HSCT)
- Imlygic (talimogene laherparepvec) important information: special considerations to minimise the potential occurrence of adverse events in HSV-1 seronegative patients receiving vials from affected lots
- Calcium Folinate 10 mg/ml solution for injection or infusion: supply of the Irish product

Medicine Recalls and Notifications

In June 2022, recalls and notifications for medicines were issued on:

Class 4 Medicines Defect Information: OxyContin 20 mg prolonged release tablets, EL (22)A/27. Issued 1 June 2022. Batches of OxyContin (oxycodone hydrochloride) 20mg prolonged release tablets have been identified to have Braille on the cartons that incorrectly states the strength as 15mg. Healthcare professionals should confirm when dispensing this product if this medicine is being collected on behalf of somebody who will solely rely on Braille, and if so, explain the error in the Braille.

Class 2 Medicines Recall: Bristol Laboratories Limited, Phenobarbital 60 mg Tablets, EL(22)A/28. Issued 13 June 2022. A batch of Phenobarbital 60mg tablets is being recalled as a precaution due to low dissolution test results reported during stability studies. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Company led medicines recall: PCCA Limited, Ketamine 50mg in 5ml Oral Solution and Ketamine 100mg in 5ml Oral Solution (unlicensed medicines), CLMR (22)A/04. Issued 15 June 2022. Batches of unlicensed ketamine 50mg in 5ml oral solution and 100mg in 5ml oral solution are being recalled due to the appearance inside the vials of a crystalline material. Healthcare professionals who have dispensed this product, should contact patients directly to return any impacted products. Stop supplying the batch immediately, quarantine all remaining stock and return to the company.

Class 4 Medicines Defect Information: Altan Pharma Limited, Phenylephrine 0.08 mg/ml - solution for injection/infusion, EL(22)A/29. Issued 16 June 2022. A batch of phenylephrine (phenylephrine hydrochloride) 0.08 mg/ml solution for injection or infusion has been identified that states incorrect concentration of the phenylephrine base on the overwrapping bag label. The incorrect label states that each bag of 100ml contains 10mg of phenylephrine base, as opposed to the correct 8mg of phenylephrine base. Healthcare professionals are advised to exercise caution when using the product should refer to the label dose on the actual bag, which remains correct for this batch.

Company led medicines recall: A.Vogel Ltd, Linoforce granules 12 years plus (THR 13668/0021), CLMR (22)A/05. Issued 22 June 2022. A batch of Linoforce granules 12 years plus (whole linseed; senna leaf; frangula bark) is being recalled as a small number of packs of these pharmacy-only medicines were supplied to non-pharmacy outlets. Remaining stock of the above batch should be quarantined and returned to the company directly.

For all of the latest safety notices from the MHRA on drugs and medical devices, see Alerts and recalls for drugs and medical devices.

Sign-up to receive MHRA alerts about drugs and medical devices and subscribe to Drug Safety Update.

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