

In this edition

- [Topiramate](#) – commencement of EU review regarding potential risk of neurodevelopmental disorders in children exposed in utero
- [Mavenclad®](#) (cladribine) – new liver monitoring requirements to minimise risk of serious liver injury
- [Pregabalin](#) – expanded warning regarding drug dependence and withdrawal symptoms
- [Product information updates](#) recommended by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC)

Topiramate – commencement of EU review regarding potential risk of neurodevelopmental disorders in children exposed in utero

The European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) has commenced a [review](#) of topiramate to assess new data on a potential risk of neurodevelopmental disorders in children who have been exposed to the medicine during pregnancy¹.

Topiramate is indicated in various forms of epilepsy* and for the prophylaxis of migraine.

The current review has been initiated following the publication of a population-based cohort study² investigating 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. The study was based on Nordic registry data and included almost 4.5 million children, of which 24,825 were exposed prenatally to at least one AED, including 471 who were exposed to topiramate monotherapy. 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.

In light of this important new information, the PRAC is undertaking an in-depth evaluation of these potential risks, including to determine the need for further risk minimisation advice, to raise awareness and to prevent exposure to topiramate during pregnancy.

Healthcare professionals (HCPs) are reminded that product information** for topiramate already includes warnings and restrictions regarding use in pregnancy and in women of childbearing potential. The use of topiramate by pregnant women is already known to increase the risk of major congenital abnormalities (3-fold compared with a reference group not taking AEDs) and foetal growth restriction (low birth weight and small for gestational age) in children exposed in-utero. Therefore, topiramate is already contraindicated for use as migraine prophylaxis in pregnancy and in women of childbearing potential if not using a highly effective method of contraception.

In the treatment of epilepsy, specialist advice should be given to women who are of childbearing potential and consideration of alternative therapeutic options is recommended. In women being treated for epilepsy with topiramate, sudden discontinuation of therapy should be avoided as this may lead to breakthrough seizures.

Before the initiation of treatment with topiramate in a 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.

If a woman plans a pregnancy, a preconceptional visit is recommended in order to reassess the treatment, and to consider other therapeutic options.

Pending the outcome of the PRAC evaluation, HCPs should also take into account the potential risk of neurodevelopmental disorders when prescribing and discussing topiramate therapy with women of childbearing potential and in case of pregnancy.

Key Message

A recently published study reported an association between prenatal exposure to topiramate and an increased risk of autism spectrum disorder and intellectual disability².

The EMA's safety committee has commenced a review of topiramate to assess the new information in the context of cumulative data on the risks associated with use of topiramate during pregnancy and to determine the need for further risk minimisation measures.

While the review is ongoing and pending any outcomes of the PRAC evaluation, healthcare professionals are reminded of the existing warnings and restrictions in the approved product information regarding the use of topiramate in women of child bearing potential and during pregnancy.

HCPs 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.

* Indicated as 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, and as 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.

** The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie or www.ema.europa.eu.

References:

1. European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) meeting highlights. Published July 08 2022. Available at <https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-4-7-july-2022>
2. 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.

Mavenclad® (cladribine) – new liver monitoring requirements to minimise risk of serious liver injury

A requirement for liver monitoring before initiating and during treatment has been introduced for patients taking Mavenclad® (cladribine). Liver injury, including serious cases and cases leading to discontinuation of treatment, have been reported in patients taking Mavenclad®.

Mavenclad® is indicated for the treatment of adult patients with highly active relapsing multiple sclerosis (MS). A recent review by the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) of available safety data has concluded there is an increased risk of liver injury following treatment with Mavenclad®. Most cases of liver injury concerned patients with mild clinical symptoms. However, in rare cases, a transient transaminase elevation exceeding 1000 units per litre and jaundice was described. Time to onset varied, with most cases occurring within 8 weeks after the first treatment course. The review of liver injury cases did not identify a clear mechanism. Some patients had a history of previous episodes of liver injury with other medicines or had underlying liver disorders. Data from clinical trials did not suggest a dose-dependent effect.

Liver injury has now been included in the product information of Mavenclad® as an adverse drug reaction of uncommon frequency. The product information* has been updated with new warnings and precautions regarding liver injury, including recommendations to obtain patient history for underlying liver disorders or previous liver injury, and to assess liver function prior to treatment initiation in year 1 and 2. In addition to the product information, educational materials (a [prescribers' guide](#) and a [patient guide](#)) that are available for healthcare professionals and patients to support the safe prescription and use of Mavenclad® have been updated.

Advice to Healthcare Professionals

- Before initiating treatment, a detailed patient history of underlying liver disorders or episodes of liver injury with other medicines should be undertaken.
- Patients should have liver function tests including assessment of serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to initiation of therapy and in year 1 and year 2. During treatment, liver function tests should be conducted, and repeated as necessary.
- In case a patient develops liver injury, treatment with Mavenclad® should be interrupted or discontinued, as appropriate. Patients should be advised to seek urgent medical attention if they experience any clinical features of liver injury.

Key Message

Liver injury, including serious cases, has been reported in patients treated with Mavenclad® (cladribine).

Before initiating treatment with Mavenclad®, a detailed hepatic patient history should be undertaken.

Liver function tests should be performed prior to initiation of therapy in year 1 and year 2, and during treatment they should be repeated as necessary.

Advise patients to seek urgent medical attention if they develop any clinical features of liver injury.

If a patient develops liver injury, treatment with Mavenclad® should be interrupted or discontinued, as appropriate.

* The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie or www.ema.europa.eu.

Pregabalin – expanded warning regarding drug dependence and withdrawal symptoms

Pregabalin-containing medicinal products* are authorised in Ireland and across the EU for the treatment of neuropathic pain in adults, as adjunctive therapy in adults for specific forms of epilepsy, and for generalised anxiety disorder in adults.

Product information** for pregabalin already includes a warning that cases of misuse, abuse and dependence have been reported and that caution should be exercised in patients with a history of substance abuse. Following a review of available data, the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) has expanded the warning to reflect that pregabalin can cause drug dependence, and that this may occur at therapeutic doses. Patients with a history of substance abuse may be at higher risk for pregabalin misuse, abuse and dependence.

Healthcare professionals (HCPs) should carefully evaluate an individual patient's risk of misuse, abuse and dependence before prescribing pregabalin. Patients treated with pregabalin should be monitored for symptoms of misuse, abuse or dependence, such as development of tolerance, dose escalation and drug-seeking behaviour.

The occurrence of withdrawal symptoms following discontinuation of pregabalin may indicate drug dependence. Symptoms reported include insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness. Patients prescribed pregabalin should be informed of this at the start of the treatment. If pregabalin is discontinued, it is recommended this should be done gradually over a minimum of one week independent of the indication.

HCPs are reminded that pregabalin has also been associated with severe respiratory depression, including in the absence of concomitant opioid or other CNS depressant use in patients with and without risk factors for respiratory depression, as highlighted in [HPRA Drug Safety Newsletter Edition 105](#). Dose adjustments may be necessary in patients at higher risk of respiratory depression (e.g. patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants, and in those of older age).

Key Message

Pregabalin can cause drug dependence, which may occur at therapeutic doses.

Patients with a history of substance abuse may be at a higher risk of pregabalin misuse, abuse and dependence.

Patients prescribed pregabalin should be monitored for symptoms of misuse, abuse and dependence.

The occurrence of withdrawal symptoms following discontinuation of pregabalin may indicate dependence.

Patients prescribed pregabalin should be informed of this risk prior to commencing treatment.

If pregabalin is to be discontinued, it is recommended this should be done gradually, over a minimum of one week, independent of the indication.

* Further details on pregabalin-containing medicines including Lyrica and generics are available at www.hpra.ie or www.ema.europa.eu.

** The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie and www.ema.europa.eu.

Product information updates recommended by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC)

The HPRA is highlighting a selection of recommendations, made by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), to update product information for medicines in clinical use. The PRAC, in which the HPRA participate, are responsible for assessing and monitoring the safety of medicines. Healthcare professionals (HCPs) are reminded to regularly check the [HPRA](http://www.hpra.ie) or [EMA](http://www.ema.europa.eu) websites for current product information concerning medicines they prescribe or dispense.

Methylphenidate-containing medicines: small increased risk of cardiac malformations in infants exposed during the first trimester of pregnancy

Methylphenidate is a centrally acting sympathomimetic which is indicated in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children between 6 and 18 years and also adults

- Data from a large cohort study¹ of approximately 3,400 pregnancies has shown a small increased occurrence of cardiac malformations (pooled adjusted relative risk, 1.3; 95% CI, 1.0-1.6) in infants exposed to methylphenidate during the first trimester of pregnancy compared with non-exposed pregnancies. However, the study did not show an increased risk of overall birth defects. The product information* has been updated to reflect the data.
- HCPs are reminded that methylphenidate-containing medicines are not recommended for use during pregnancy unless there is a clinical decision that postponing treatment may pose a greater risk to the pregnancy.

Reference

1. Huybrechts K, Broms G, Christensen L, et al. Association between methylphenidate and amphetamine use in pregnancy and risk of congenital malformations. *JAMA Psychiatry* December 2017.

Hormonal contraceptives: updated warning regarding depressed mood and depression

Hormonal contraceptives are licensed in Ireland in various presentations including oral tablet, transdermal patch, subdermal implant, vaginal ring and intrauterine delivery device, and are available as combined or single ingredient (progesterone only) presentations.

- Depressed mood and depression are known potential adverse reactions to hormonal contraceptive use, and are already described in product information. The product information* for hormonal contraceptives has now been updated to reflect that depression can be serious and that this is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms including shortly after initiating treatment with a hormonal contraceptive.
- This update applies to both combined hormonal contraceptives and progesterone-only hormonal contraceptives.

* The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie and www.ema.europa.eu.

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Dexmedetomidine	Increased risk of mortality in intensive care unit (ICU) patients \leq 65 years
Defitelio (defibrotide)	Do not use for prophylaxis of veno-occlusive disease (VOD) after post hematopoietic stem cell transplantation (HSCT)
Oclavia[▼] (obeticholic acid)	New contraindication for the treatment of primary biliary cholangitis (PBC) in patients with decompensated liver cirrhosis or a history of prior hepatic decompensation
Rubraca[▼] (rucaparib)	Interim data from study (ARIEL4) show a decrease in overall survival compared to standard of care

Reporting suspected adverse reactions

Healthcare professionals are encouraged to report suspected adverse reactions to the HPRA via the available options at www.hpra.ie/report, which include an [online report form](#).

All reports submitted to the HPRA are reviewed and stored on the HPRA's national adverse reaction database. They are subsequently submitted to the EMA's EudraVigilance database where they are available for analysis and to support early detection and monitoring of possible safety signals*.

Reporting suspected adverse reactions, even those known to occur in association with a medicine, adds to knowledge about the frequency and severity of these reactions and can help to identify patients who are most at risk.

* A privacy notice relating to the processing of personal data collected by the HPRA in relation to adverse reaction reports is available on the [HPRA website](#).