April 2024

HPRA DRUG SAFETY
NEWSLETTER

115TH EDITION

In this edition

- Valproate (Epilim▼): New precautionary measures regarding the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months before conception
- NSAIDs: Updated recommendations on the use of non-steroidal anti-inflammatory drugs (NSAIDs) during pregnancy
- Cystic Fibrosis transmembrane conductance regulators (CFTRs): New warning on the risk of depression and related events associated with Kalydeco, Orkambi, Symkevi and Kaftrio
- Product information updates recommended by the EMA's Pharmacovigilance Risk assessment Committee (PRAC)

Valproate (Epilim▼): New precautionary measures regarding the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months before conception

Key Message

- A retrospective observational study in three Nordic countries suggests an increased risk of neurodevelopmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the three months before conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy. Due to study limitations, this risk is considered possible but has not been confirmed. As a precaution, new measures are being introduced to inform patients and healthcare professionals of this potential risk.
- Prescribers should inform male patients about the potential risk and discuss with them the need to consider effective contraception, including for a female partner while using valproate and for three months after stopping the treatment.
- Regularly review treatment in male patients to evaluate whether valproate remains the most suitable treatment for the patient.
- For male patients planning to conceive a child, suitable alternative treatment options should be considered and discussed with the patient. Individual circumstances should be evaluated for each patient.
- Male patients should be advised not to donate sperm during treatment and for at least three months after treatment discontinuation.
- It is recommended that in male patients, valproate is initiated and supervised by a specialist experienced in the treatment of epilepsy or bipolar disorder.

1 Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

Background information

Valproate-containing medicines are approved nationally in Ireland with various presentations under the brand name Epilim for treatment indications in epilepsy and bipolar disorder*.

The HPRA previously published an article in Edition 113 of this newsletter regarding an ongoing review at that time by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) of a study to investigate the risk of neurodevelopmental disorders (NDDs) in offspring paternally exposed to valproate as monotherapy, compared to lamotrigine or levetiracetam as monotherapy treatment, in the three months before conception. At that time, the PRAC had requested the pharmaceutical companies involved in this study to provide re-analyses of corrected data, as some errors had been noted, as well as additional information and analyses to address study limitations. The PRAC has now completed its evaluation of the corrected data and has recommended new precautionary measures concerning the use of valproate in male patients.

The study (EUPAS34201) was conducted by pharmaceutical companies of valproate-containing products as an obligation following a previous EU-wide review of valproate use during pregnancy. This retrospective observational study used data from multiple registry databases in Denmark, Sweden and Norway[1,2]. The primary outcome of interest was NDDs (composite endpoint including autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders, and movement disorders) in offspring up to 11 years of age. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group.

- The meta-analysis of data from the three countries resulted in a pooled adjusted hazard ratio of 1.50 (95% CI: 1.09-2.07) for NDDs in children from fathers treated with valproate monotherapy in the three months before conception compared to the composite lamotrigine/levetiracetam monotherapy group.
- The adjusted cumulative risk of NDDs ranged between 4.0% and 5.6% in the valproate group monotherapy versus between 2.3% and 3.2% in the composite lamotrigine/levetiracetam monotherapy group.

The study was not large enough to investigate associations with specific NDD subtypes. Due to study limitations, including potential confounding by indication and differences in follow-up time between exposure groups, the risk of NDDs in children of fathers who used valproate in the three months before conception is considered a potential risk and a causal association with valproate is not confirmed. Nonetheless, considering the available data and consulting with stakeholders and experts, the PRAC considered precautionary measures warranted to inform patients and healthcare professionals[3,4].

The study did not evaluate the risk of NDD in children born to men who had discontinued valproate treatment for more than three months before conception (i.e. allowing a new spermatogenesis without valproate exposure).

The observed potential risk of NDDs after paternal exposure in the three months before conception is of a lower magnitude than the known risk for NDDs after maternal exposure during pregnancy. When valproate is administered as monotherapy to women, studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development, such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Based on the available data, new measures for valproate use in men have been adopted. A Direct Healthcare Professional Communication (DHPC) has also been sent to inform healthcare professionals of the review's outcome and the new precautionary measures for male patients.

Advice for healthcare professionals

- Prescribers should inform male patients about the potential risk and discuss with them the need to consider effective contraception, including for a female partner while using valproate and for three months after stopping the treatment.
- Regularly review treatment with valproate in male patients to evaluate whether valproate remains the most suitable treatment for the patient.
- For male patients planning to conceive a child, suitable alternative treatment options should be considered and discussed with the patient. Individual circumstances should be evaluated for each patient.

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

- Male patients should be advised not to donate sperm during treatment and for at least three months after treatment discontinuation.
- It is recommended that in male patients, valproate is initiated and supervised by a specialist experienced in the treatment of epilepsy or bipolar disorder.

New educational materials for males

The PRAC's latest recommendations come in addition to restrictions and other measures already in place to avoid exposure to valproate during pregnancy from maternal use as part of the PREVENT pregnancy prevention programme.

The product information of all valproate-containing medicines is updated to inform healthcare professionals and patients of the potential risk of NDD in children of men treated with valproate and to provide guidance regarding the use of valproate in men. In addition, educational materials will be available for healthcare professionals. These include:

- A new patient guide for men outlining information on the potential risk, which should be provided to male patients using valproate.
- An update of the existing patient card with information for male patients, which will be attached to the outer packaging of Epilim packs, so that it will be provided in the pharmacy to the patient each time the medicine is dispensed.
- The existing guide for healthcare professionals for valproate's PREVENT pregnancy prevention programme will be updated to include a dedicated section on the use of valproate in male patients.

Hard copies of the educational materials will be disseminated by the licensing holder in Ireland following approval by the HPRA. Copies will also be published on the HPRA's valproate special topics page and can be found using the Find a medicine search. It is anticipated that these materials will be available by June.

* *Valproate product information and educational materials are available at www.hpra.ie*

References

1. A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring – a population-based retrospective study. (2023). [online] IQVIA. Available at: https://catalogues.ema.europa.eu/system/files/2024-02/Valproate_PASS_Protocol_V7.0.PDF.
2. PASS -Paternal exposure to valproate -Updated Abstract Following Reanalysis of Norway Data of Corrigendum to Final Study Report Version 1.1 and Addendum Version 2 Valproate EU consortium Stand Alone Abstract V2.0. (n.d.). Available at: https://catalogues.ema.europa.eu/system/files/2024-02/Valproate_PASS_Abstract_V2.0_0.pdf
3. PRAC non-interventional imposed PASS final study report assessment report. (2024). [online] European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/other/valproate-prac-non-interventional-imposed-pass-final-study-report-assessment-report-emea-h-n-psr-j-0043_en.pdf.
4. Potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines: PRAC recommends precautionary measures | European Medicines Agency. [online] Available at: https://www.ema.europa.eu/en/news/potential-risk-neurodevelopmental-disorders-children-born-men-treated-valproate-medicines-prac-recommends-precautionary-measures.
5. HPRA special topics. EMA recommends precautionary measures following review of study in children whose fathers were treated with valproate. Available at: https://www.hpra.ie/homepage/medicines/special-topics/valproate-(epilim)/valproate-(epilim-)-ema-review-of-study-in-children-whose-fathers-were-treated-with-valproate.
6. Sanofi (2024). Valproate - containing medicines: new measures regarding the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception. Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-valproate---containing-medicines.pdf?sfvrsn=0.

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie **www.hpra.ie**

Updated recommendations on the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) during pregnancy

Key Message

The EMAs Pharmacovigilance Risk Assessment Committee (PRAC) has issued updated recommendations following a review of recently available data that indicates that from the 20th week of pregnancy onward, prolonged use of systemic NSAIDs may lead to oligohydramnios due to foetal renal dysfunction. Additionally, there have been reports of ductus arteriosus constriction following NSAID treatment during the second trimester, with most cases resolving after treatment cessation.

Systemic NSAIDs

- During the first and second trimesters of pregnancy, systemic NSAIDs (including fixed-dose combinations) should not be administered unless deemed clearly necessary.
- For women attempting to conceive or during the first and second trimesters, the dose should be kept as low as possible, and treatment duration should be minimised.
- Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to NSAIDs for several days from gestational week 20 onward. If oligohydramnios or ductus arteriosus constriction is detected, NSAID treatment should be discontinued promptly.
- If the product information already contains stricter advice regarding the use of NSAIDs during pregnancy, the stricter advice should be followed.
- Healthcare professionals are reminded that currently, the used of systemic NSAIDs is contraindicated in the last pregnancy trimester.

Topical NSAIDs

- The PRAC has recommended that the same precautions regarding the use, dosage, and duration of treatment for systemic NSAIDs be observed for topical NSAIDs.

Acetylsalicylic acid

- The PRAC has not issued these recommendations for acetylsalicylic acid-containing products at this time.

Background information

The EMA's PRAC has recommended that the approved product information* for systemic (i.e. oral and injectable) NSAID-containing medicinal products, including fixed-dose combinations, should be updated with regard to the use of these products during pregnancy. The updates follow the review of available data which concluded that the use from the 20th week of pregnancy onward may cause oligohydramnios resulting from foetal renal dysfunction. It was observed that this may occur shortly after treatment initiation and was usually reversible upon treatment discontinuation. Additionally, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

The PRAC recommendations for systemic NSAIDs during pregnancy

During the first and second pregnancy trimesters, systemic NSAIDs should not be given unless deemed clearly necessary. If the NSAID is deemed necessary, the dose should be kept as low and the duration of treatment as short as possible. This recommendation also applies to a woman attempting to conceive.

Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to NSAIDs for several days from gestational week 20 onward. The NSAID should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

While the product information for NSAIDs will be amended to include updated advice for use during pregnancy, when stricter advice on use in pregnancy already exists, the stricter advice will remain.

These new recommendations primarily concern the first and second pregnancy trimesters; currently, the use of systemic NSAIDs is contraindicated in the last trimester of pregnancy as they may induce foetal cardiopulmonary and renal toxicity, inhibit uterine contraction, leading to delayed or prolonged labour and possibly extend the bleeding time for mothers and neonates due to anti-aggregating effects that may occur even at very low doses.

New recommendations for topical NSAIDs in pregnancy

Following several routine reviews of available data concerning medicines within the same therapeutic class, the PRAC concluded that although systemic exposure with the use of topical NSAIDs (including oromucosal formulations and transdermal patches) is typically lower compared to oral administration, it could not definitively exclude the potential risk of oligohydramnios and ductus arteriosus to the embryo/foetus.

Consequently, to date the PRAC recommended updating the product information for several topical NSAIDs, including naproxen, ketoprofen, ibuprofen and flurbiprofen products. It is recommended to avoid the use of topical NSAID products during the first and second pregnancy trimesters unless deemed clearly necessary. If deemed necessary, the dosage should be kept as low and the treatment duration as short as possible. As is the case for systemic NSAIDs, use of topical NSAIDs is contraindicated during the last trimester of pregnancy.

Healthcare professionals are advised to check relevant product information when considering the use of topical NSAIDs during pregnancy, as it is already recommended to avoid certain topical NSAIDs, like ibuprofen, during pregnancy.

Implication for Acetylsalicylic Acid-containing Products

Due to the different clinical applications and dosages of acetylsalicylic acid-containing products and the need to evaluate the available data and the implications of the NSAID recommendations, acetylsalicylic acid-containing products are currently excluded excluded from the implementation of PRAC recommendations to date.

* *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*

New warning on the risk of depression and related events associated with Kalydeco, Orkambi, Symkevi and Kaftrio

Key Message

- Depression (including suicidal ideation and suicide attempt) has been reported in patients treated with these medicines, usually within three months of treatment initiation, and in patients with a history of psychiatric disorders.
- In some cases, symptom improvement was reported after dose reduction or treatment discontinuation.
- Patients (and caregivers) should be alerted to the need to monitor for depressed mood, suicidal thoughts, or unusual changes in behaviour.

Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symkevi (tezacaftor/ivacaftor), and Kaftrio (elexacaftor/tezacaftor/ivacaftor) are cystic fibrosis transmembrane conductance regulator (CFTR) modulators authorised in the EU for the treatment of cystic fibrosis*. The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has recommended updates to the product information** for these medicines to include a new warning on the risk of depression.

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

The recommendation follows a review of the available data on the risk of depression and related events, including cases from spontaneous reports in post-marketing surveillance, some with a close temporal relationship and a positive de-challenge and re-challenge, and based on which the PRAC considered that a causal relationship is at least a reasonable possibility.

Depression (including suicidal ideation and suicide attempt) has been reported in patients, usually occurring within three months of treatment initiation and in patients with a history of psychiatric disorders. In some cases, symptom improvement was reported after dose reduction or treatment discontinuation.

Patients (and caregivers) should be alerted to the need to monitor for depressed mood, suicidal thoughts, or unusual changes in behaviour, and to seek medical advice immediately if these symptoms present.

The summary of product characteristics and package leaflet for these medicines has been updated accordingly.

* *Please refer to product information for further details on authorised indications, available at 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.ema.europa.eu.*

Product information updates recommended by Pharmacovigilance Risk Assessment Committee

The HPRA is highlighting a selection of recommendations, made by the PRAC, to update product information for medicines in clinical use. The PRAC, in which the HPRA participate, is responsible for assessing and monitoring the safety of medicines. HCPs are reminded to regularly check the HPRA or EMA websites for current product information concerning medicines.

HMG-CoA reductase inhibitors (statins): potential for statins to aggravate myasthenia gravis.

HMG-CoA reductase inhibitors are licenced for the reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides.

- Product information for statin-containing products has been updated to highlight that in a few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia.
- Statin-containing products should be discontinued if symptoms of existing myasthenia gravis or ocular myasthenia should be aggravated.
- Recurrences of these reactions have also been reported when the same or a different statin was (re-) administered.

Rivaroxaban (Xarelto) and Edoxaban (Lixiana): Anticoagulant-related nephropathy added as an adverse reaction.

Rivaroxaban and Edoxaban are anticoagulant medicines indicated for use in various indications, such as for the prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

- Anticoagulant-related nephropathy has been added as an adverse reaction to section 4.8 of the SmPC with a frequency of 'not known' as a known complication secondary to severe bleeding.
- Product information already reflects other known complications secondary to severe bleeding, such as compartment syndrome and renal failure due to hypoperfusion. The package leaflet has also been updated accordingly.

Edoxaban (Lixiana): Drug-drug interaction (DDI) with clarithromycin.

- Information on drug-drug interaction between clarithromycin and edoxaban has been added to the Summary of Product Characteristics, specifically that clarithromycin (500mg twice daily) for ten days with a single concomitant dose of edoxaban 60mg on day 9 increased the edoxaban plasma area under the curve (AUC) and maximum serum concentration (Cmax) by approximately 53% and 27%, respectively.
- Concomitant use of edoxaban with clarithromycin does not require a dose adjustment.
- The package leaflet will advise patients to inform their healthcare professional if they are or have taken antibiotic medicines, such as clarithromycin.

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

PRODUCT	SAFETY ISSUE
Pseudoephedrine	Risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS).
Valproate	New measures regarding the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception.
Paxlovid (nirmatrelvir; ritonavir)	Reminder of life-threatening and fatal drug-drug interactions with certain immunosuppressants, including tacrolimus.

Reporting suspected adverse reactions

Healthcare professionals are encouraged to report suspected adverse reactions to the HPRA via the available options at http://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 the to the processing of personal data collected by the HPRA in relation to adverse reaction reports is available on the HPRA website

Correspondence/comments should be sent **by email only** to the Pharmacovigilance Section, Health Products Regulatory Authority, medsafety@hpra.ie.

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority