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HPRA DRUG SAFETY NEWSLETTER

81ST EDITION

In this Edition

Valproate (Epilim) and Developmental Disorders: Update on ongoing EU review

Babies born to mothers who take valproate-containing medicines (Epilim) during pregnancy have a 30–40% risk of developmental disability and a 10% risk of birth defects. The HPRA issued communications in its Drug Safety Newsletter (DSN) (editions 65, 76, and 80) on the magnitude of this risk and the actions to take. Further to the HPRA update in the last edition of the DSN, we are now informing you that the ongoing EU review is considering whether further regulatory action is necessary and there will be a public hearing at the European Medicines Agency (EMA) on September 26th 2017. More information about the registration process for the public hearing is available on the EMAs website.

Risks of exposure in pregnancy and previous communications:

Babies exposed to valproate in utero are at a very high risk of developmental disorders and congenital malformations. In October 2014 and August 2016, the HPRA advised against prescribing valproate-containing medicines in girls and women of childbearing potential, unless other treatments are ineffective or not tolerated. In August 2016, we issued further communication materials and resources to support discussion of these risks with women and girls of childbearing potential who take valproate. We also collaborated with the HSE in the development of a valproate toolkit to highlight risks to the unborn child and to support the safety of girls and women taking valproate. Educational materials developed by the Marketing Authorisation Holder (MAH), following HPRA approval to inform healthcare professionals and patients about these risks are also available from the HPRA website and the MAH. The HPRA is aware that a contraindication on the use of valproate for bipolar disorder during pregnancy and in women of childbearing potential not using effective contraception has been introduced in France. The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA has been kept aware of this action, which is based on the same data used to trigger its ongoing review. The PRAC has already stated that valproate should never be used in pregnancy or in women of childbearing potential not using effective contraception, unless there is no alternative. Further EU-wide recommendations aiming to ensure the most appropriate use of these medicines in all their indications will be made in the next few months and the HPRA will again highlight the results of the current review of the use of valproate-containing medicines and further recommendations, when they are announced.

Reminder of advice to Healthcare Professionals

- Babies born to mothers who take valproate during pregnancy have a 30–40% risk of developmental disability and a 10% risk of birth defects. Valproate must not be prescribed for epilepsy or bipolar disorder in women and girls unless other treatments are ineffective or not tolerated; migraine is not a licensed indication.
- Valproate use in women and girls of childbearing potential must be initiated and supervised by specialists in the treatment of epilepsy or bipolar disorder.
- Women of childbearing potential must use effective contraception during treatment.
- Ensure women and girls taking valproate understand the 30-40% risk of neurodevelopmental disorders and 10% risk of birth defects and are using effective contraception.
- Prescribers should carefully reconsider the benefit and risk of treatment with valproate particularly at the time of puberty in girls, and at regular treatment reviews thereafter, and urgently when a woman treated with valproate plans a pregnancy, or if she becomes pregnant.
- In women who are currently on valproate and are planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

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Key Message

Valproate is associated with a high teratogenic potential and a high risk of developmental disorders in infants exposed in utero to valproate.

Women of childbearing potential must use effective contraception during treatment.

In women who are currently on valproate and are planning to become pregnant or become pregnant, all efforts should be made to switch to appropriate alternative treatment, if possible.

All suspected adverse reactions associated with valproate should be reported to the HPRA via the usual methods (www.hpra.ie).

Valproate-containing medicines are approved nationally in Ireland in various presentations, under the brand name Epilim, to treat epilepsy and bipolar disorder. Further information on valproate-containing medicines is available from www.hpra.ie.

Domperidone-containing medicines: reminder of the risk of cardiac adverse reactions-restricted indication, contraindications and reduced dose and duration of use

In 2014 a European-wide review recommended restrictions on the use of domperidone-containing medicines following an evaluation of the benefits and risks of domperidone. This review was triggered due to concerns regarding cardiac adverse effects associated with domperidone use.

After evaluation of available evidence on the efficacy and safety of domperidone from various sources (non-clinical and clinical, published and unpublished), the review confirmed that there was a small increased risk of serious cardiac adverse effects associated with the use of domperidone, including QT-prolongation, torsades de pointes, ventricular arrhythmia and sudden cardiac arrest. This risk was higher in patients > 60 years, adults taking daily oral doses of >30 mg and those concomitantly taking QT-prolonging medicines or CYP3A4 inhibitors. The review concluded that the benefit-risk profile remains positive in the treatment of nausea and vomiting, when there is adherence to the risk minimisation measures set out in the product information.

Domperidone should be used at the lowest effective dose for the shortest possible duration (not exceeding 1 week). The maximum recommended dose of domperidone in adults is 10 mg orally up to 3 times daily or 30 mg twice daily as suppositories. The recommended dose of domperidone for children is 0.25mg/kg bodyweight up to 3 times daily orally (oral suspensions should be given in adapted graduated oral syringes).

Domperidone is contraindicated in patients with moderate or severe hepatic impairment, conditions where cardiac conduction is, or could be, impaired, patients with underlying cardiac disease. Co-administration with QT-prolonging medicines or potent CYP3A4 inhibitors is also contraindicated.

Healthcare Professionals are reminded of the following advice to support the safe and appropriate use of domperidone:

Reminder of restricted indication

- The use of domperidone is restricted to the relief of symptoms of nausea and vomiting.

Reminder of contraindications

Domperidone should not be used in:

- patients with conditions where cardiac conduction is, or could be, impaired,
- patients with underlying cardiac diseases such as congestive heart failure,
- patients receiving other medications known to prolong QT interval or potent CYP3A4 inhibitors, and
- patients with moderate to severe hepatic impairment.

Reminder of the restrictions on dose

Oral formulations

- For adults and adolescents over 12 years of age and weighing 35kg or more, the recommended maximum dose in 24 hours is 30mg (dose interval: 10mg up to three times a day).
- In children under 12 years of age and weighing less than 35kg, the recommended maximum dose in 24 hours is 0.75mg/kg body weight (dose interval: 0.25mg/kg body weight up to three times a day).
- In order to accurately measure doses to paediatric patients, oral suspensions should be given using an adapted graduated oral syringe.

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Suppository formulation

- Suppositories should only be used in adults and adolescents weighing 35kg or more, the recommended maximum daily dose in 24 hours is 60mg (dose interval: 30mg twice a day).
- Note: there are currently no suppository formulations of domperidone authorised in Ireland.

Reminder of the duration of treatment

- Domperidone should be used at the lowest effective dose for the shortest possible duration.
- The maximum treatment duration should not usually exceed one week.
- Patients currently receiving long-term treatment with domperidone should be reassessed at a routine appointment to advise on treatment continuation, dose change, or cessation.

Key Message

Domperidone is associated with a small increased risk of serious cardiac adverse reactions.

HCPs are reminded of the following risk minimisation measures:

Therapeutic Indications: Use of domperidone is restricted to the relief of symptoms of nausea and vomiting.

Contraindications: Domperidone is contraindicated in patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure, in patients who are concomitantly taking QT-prolonging drugs or potent CYP3A4 inhibitors (regardless of their QT-prolonging effects) and in patients who have moderate or severe hepatic impairment.

Dose and duration of use: HCPs should adhere to the dose and duration of use for adults, adolescents and children recommended in the Summary of Product Characteristics. Patients >60 years of age should consult a Healthcare Professional before taking domperidone. Domperidone should be used at the lowest effective dose for the shortest duration necessary. The maximum treatment period should not usually exceed one week.

**Products currently authorised in Ireland include Motilium and Domerid. Further details are available at www.hpra.ie*

New CPD e-learning module on reporting suspected adverse drug reactions

A new free e-learning module has been created for all healthcare professionals to learn about the importance of reporting suspected adverse drug reactions (ADRs). This module was created as part of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action project. The module has received accreditation from the European Accreditation Council for CME (EACCME®). Doctors are awarded 1 EACCME credit (1 hour) upon completion of the 45 minute ADR e-learning module. The SCOPE Joint Action project, in which the Health Products Regulatory Authority (HPRA) participated, aims to support EU member states in the operation of their pharmacovigilance systems which help safeguard public health.

The e-learning module covers important topics relating to the reporting of suspected ADRs, including how to report and what happens to a report once it is made; who can make a report; situations in which a report should be made; and sources of information on ADRs. The e-learning module (hosted on the SCOPE website) can be accessed by clicking here.

There are several options in place for reporting suspected ADRs to the HPRA. These are as follows:

- By following the links ('Report an Issue' tab) to the online reporting options accessible from the HPRA website homepage (www.hpra.ie);
- Using the downloadable report form also accessible from the HPRA website, which may be completed manually and submitted to the HPRA via 'freepost';
- Using the traditional 'yellow card' report, which also utilises a freepost system. 'Yellow cards' are available from the HPRA Pharmacovigilance department on request.
- By telephone to the HPRA Pharmacovigilance section (01-6764971).

Further details on reporting of suspected ADRs to the HPRA can be found on the HPRA website or in a recent article in the 79th edition of the HPRA Drug Safety Newsletter.

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Advice to Healthcare Professionals

- Reporting suspected ADRs aids in facilitating continued surveillance of the safety of medicines.
- Reports of suspected ADRs can be made by all healthcare professionals and patients/members of the public to the HPRA.
- A suspicion that a medicine caused a reaction is sufficient to warrant a report.
- Healthcare professionals and patients are particularly encouraged and reminded to report all ADRs associated with the use of medicines subject to additional monitoring. These medicines are identifiable by an inverted black triangle and explanatory statement on the product information i.e. the Summary of Product Characteristics (SmPC) and Package Leaflet (PL):▼ This medicinal product is subject to additional monitoring.

Key Message

A free e-learning module for healthcare professionals on reporting suspected ADRs is available on the SCOPE website (http://www.scopejointaction.eu/) or by clicking here.

Doctors can earn 1 EACCME credit upon completion of the 45 minute ADR e-learning module.

Further information on the reporting of suspected ADRs and the role of the HPRA is available from www.hpra.ie.

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

PRODUCT	SAFETY ISSUE
Zinbryta (daclizumab)	Restrictions of use of Zinbryta (daclizumab) in view of fatal fulminant liver failure.
Uptravi (selexipag)	Concomitant use with strong CYP2C8 inhibitors (e.g. gemfibrozil) is now contraindicated.
Clexane (enoxaparin sodium)	Updates to strength expression, dose regimens in DVT/PE, use in patients with severe renal impairment.
Levact (bendamustine)	Increased mortality, serious & fatal infections, reactivation of Hepatitis B, prolonged lympocytopenia and low CD4-positive T-cell counts observed in recent clinical studies with Levact (bendamustine).
Cotellic (cobimetinib)	Important additional warnings for hemorrhage and rhabdomyolysis with Cotellic (cobimetinib), including new dose modification recommendations.

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.

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