HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

TERATOGENICITY OF VALPROATE-CONTAINING MEDICINES (EPILIM▼) – REMINDER OF IMPORTANT RESTRICTIONS FOR USE IN WOMEN AND GIRLS

Healthcare professionals (HCPs) will be aware that valproate-containing medicines (licensed in Ireland as Epilim▼) have a high teratogenic potential. According to studies, children exposed in utero have up to a 30-40% risk of developmental disorder and an approximate 10% risk of congenital malformations. Evidence characterising these risks continues to emerge, and the product information for Epilim▼ was recently updated to reflect the availability of new scientific information in this regard. This included information regarding the risk of hearing impairment or deafness (unilateral or bilateral) due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on hearing function associated with exposure in utero.

Due to the known teratogenic effects, Epilim▼ should not be used in female children and women of childbearing potential[1] (WCBP), unless other treatments are ineffective or not tolerated. Treatment must be initiated and supervised by a suitably experienced specialist[2]. In addition, use in WCBP in any indication (epilepsy, bipolar) is **contraindicated** unless the conditions of a pregnancy prevention programme (called **prevent**) are fulfilled. The purpose of this article is to remind HCPs of the high teratogenic potential of Epilim▼, to highlight the conditions of the **prevent** programme and the availability of additional information and resources to support safe and appropriate use.

Valproate Pregnancy Prevention Programme – prevent

Prevent was put in place in 2018, on the recommendation of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC), as previous measures taken in 2014 had not been sufficiently effective in practice.

The **prevent** programme was designed to further ensure female patients, who require treatment with Epilim▼, have an understanding of the risks and the need to avoid becoming pregnant during treatment. Conditions of the programme include (but are not limited to) the need for highly effective contraception[3] throughout treatment, pregnancy testing prior to initiation (and as required during treatment), an annual specialist review of the continued appropriateness of treatment with Epilim▼, a review of the risks with individual patients, pregnancy planning and pregnancy management.

For **prevent** to be effective, it is essential that HCPs are aware of their respective responsibilities and ensure implementation of actions necessary to minimise the risk in practice. HCPs must ensure that their patients remain fully informed of appropriate treatment options and understand the risks of in utero exposure to valproate for an unborn child. Full details of those actions are described in the Summary of Product Characteristics (SmPC), as well as in an educational guide for HCPs, which are available from the HPRA website. The key messages of the HCP guide were recently summarised in the 97th Edition of the HPRA's Drug Safety Newsletter, which is also available from the HPRA website.

Summary of teratogenic risks

- Valproate-containing medicines (licensed in Ireland as Epilim▼) have a high teratogenic potential. According to studies, children exposed in utero have up to a 30-40% risk of developmental disorder and an approximate 10% risk of congenital malformations.
- The risk of adverse effects on the mental and physical development of exposed children seems to be dose-dependent but a threshold dose, below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.
- Developmental disorders seen in children include delays in early development, lower intellectual abilities and IQ, poor language skills, memory problems. Data on the long-term outcomes is more limited.

- Available data from population based studies show that children exposed in utero are at an increased risk of autistic spectrum disorder and childhood autism, and also of developing symptoms of attention deficit/hyperactivity disorder (ADHD) compared to the unexposed population in the studies.
- In relation to congenital malformations, the most commonly reported types include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.
- The product information for Epilim▼ was recently updated to reflect evidence that in utero exposure may result in hearing impairment or deafness (unilateral or bilateral) due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function.

Further information

The educational materials for Epilim▼ and the **prevent** programme were recently updated. A DHPC outlining the updates was distributed in August 2020. A copy of all materials are available on the HPRA website, and include:

- An Annual Risk Acknowledgement Form to be used at the time of treatment initiation and during each annual review of valproate treatment by the specialist.
- A guide for prescribers, pharmacists and other healthcare professionals potentially involved in the care of girls and women of childbearing potential treated with valproate.
- A guide for patients, which the prescriber should provide to all girls and WCBP who start treatment with valproate or who are already on treatment.
- A patient reminder card attached to the outer packaging of valproate-containing medicines to facilitate discussions between the pharmacist and the patient each time the medicine is dispensed. A valproate warning sticker to be used for outer packaging (along with provision of a package leaflet) in exceptional cases where broken bulk dispensing is unavoidable.
- A pharmacy poster and pharmacy shelf barker.

Patients can also access the patient guide, patient card, Annual Risk Acknowledgement Form and most up-to-date package leaflets electronically by scanning the QR code that is printed on the Epilim package leaflet, which links to the company's Epilim QR code webpage.

[1]A woman of childbearing potential is defined as a pre-menopausal female who is capable of becoming pregnant.
[2]Specialist prescriber is defined as a consultant psychiatrist or a consultant neurologist who regularly manages bipolar disorder or complex epilepsy.
[3]At least one highly effective method of contraception (e.g. a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case and the patient should be fully involved in the discussion regarding the method of contraception chosen. Even if she has amenorrhoea she must follow all the advice on highly effective contraception.

Summary of teratogenic risks

- Valproate-containing medicines (licensed in Ireland as Epilim▼) have a high teratogenic potential. According to studies, children exposed in utero have up to a 30-40% risk of developmental disorder and an approximate 10% risk of congenital malformations.
- The risk of adverse effects on the mental and physical development of exposed children seems to be dose-dependent but a threshold dose, below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.
- Developmental disorders seen in children include delays in early development, lower intellectual abilities and IQ, poor language skills, memory problems. Data on the long-term outcomes is more limited.
- Available data from population based studies show that children exposed in utero are at an increased risk of autistic spectrum disorder and childhood autism, and also of developing symptoms of attention deficit/hyperactivity disorder (ADHD) compared to the unexposed population in the studies.
- In relation to congenital malformations, the most commonly reported types include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.
- The product information for Epilim▼ was recently updated to reflect evidence that in utero exposure may result in hearing impairment or deafness (unilateral or bilateral) due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function.

Paracetamol – Reminder to prescribers on risk of hepatotoxicity in patients with risk factors

Healthcare professionals are reminded of the known potential for hepatotoxicity in association with paracetamol, even at doses within the normal therapeutic range, in patients who are at particular risk of such adverse effects. Patients at increased risk of hepatotoxicity include patients who are underweight (adults or adolescents less than 50kg) or of low body mass index, malnourished, dehydrated, those with chronic alcoholism, co-existing renal or hepatic impairment, concomitantly taking hepatotoxic drugs and those with conditions that may predispose to glutathione deficiency or depletion. For some patients considered to be at higher risk, a lower starting dose, a reduction in dose and/or a reduced frequency of dosing may be appropriate. As some of these risk factors may change during the course of an illness (e.g. malnourishment, weight loss, dehydration), healthcare professionals should take into consideration any emerging or changing risk factors and maintain an awareness that these may warrant a dose adjustment when prescribing or administering paracetamol.