HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Valproate (Epilim ▼) – Reminder about the contraindications, warnings and measures to prevent exposure during pregnancy

Healthcare professionals (HCPs) are reminded that for valproate, epidemiological data have demonstrated that use of valproate monotherapy during pregnancy is associated with a risk of approximately 11% for major congenital malformations (MCMs) and up to 30-40% for neurodevelopmental disorders in children exposed in-utero. A threshold dose of valproate below which no risk exists cannot be established based on current evidence.

Due to the known teratogenic potential, valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated. Treatment must be initiated and supervised by a suitably experienced specialist. In addition, use in women of childbearing potential in any indication (epilepsy, bipolar disorder) is contraindicated unless the conditions of a pregnancy prevention programme (known as 'prevent') are fulfilled. Conditions of 'prevent' include:

- Discussion of the risks by the prescriber with the patient and provision of a copy of the patient guide.
- Exclusion of pregnancy by serum pregnancy test prior to initiation of treatment.
- Arrange for highly effective contraception for women of childbearing potential before the first prescription is issued.
- Ensure continuous use of highly effective contraception in all women of childbearing potential (consider the need for pregnancy testing if not a highly effective method).
- Review of treatment by a specialist at least annually.
- Completion of an Annual Risk Acknowledgement Form by the specialist and patient on treatment initiation and yearly thereafter during treatment review.
- Urgent referral to the specialist in case of unplanned pregnancy or where a patient wants to plan a pregnancy.

Valproate is contraindicated as treatment for bipolar disorder during pregnancy and as a treatment for epilepsy during pregnancy unless there is no suitable alternative.

A guide for healthcare professionals with full details regarding the 'prevent' pregnancy programme is available on the HPRA website[§]. This guide provides information about the teratogenic risks associated with the use of valproate during pregnancy, actions necessary to minimise the risks to patients and to ensure patients have an adequate level of understanding of the risk. It also provides up-to-date information about the risks of congenital malformations and neurodevelopmental disorders in children exposed to valproate during pregnancy.

A cross-sectional study was conducted in June 2019 using anonymous online surveys among general practitioners (GPs), pharmacists, and specialist consultants in Ireland to examine their awareness, knowledge, and practice in the year following implementation of the 'prevent' pregnancy prevention program for valproate[1]. The survey was sent to a random sample of HCPs, 3820 in total. Response rates were 5.8% for GPs (90/1544), 10.7% for pharmacists (219/2052), and 7.6% for specialists (17/224). Across HCP groups, in those that responded, there was high awareness (>90%) for specialist referral when female valproate patients are planning pregnancy, or become pregnant, but less awareness to refer annually for specialist review. While awareness of a possible teratogenic effect at any stage of pregnancy was high (>80%), most GPs (62.2%, 95% CI: 51.3, 71.9%) and community pharmacists (53.1%, 95% CI: 43.2, 62.8%) were unsure of the magnitude of risk for developmental disorders, while most specialists underestimated this risk (46.7%, 95% CI: 24.8, 69.9%). Although >70% of the respondents identified valproate to be contraindicated in any woman of childbearing potential unless the conditions of the pregnancy prevention program are fulfilled, experience implementing key elements in practice varied.

Whilst acknowledging the limitations of the study, including a low response rate, the findings highlight the importance of continued effort to support full implementation of 'prevent' in clinical practice. The HPRA published a special edition Drug Safety Newsletter (Edition 97) to remind HCPs of the conditions of the pregnancy prevention program, which includes a summary of the necessary actions for specialists, GPs and pharmacists to take (see the HPRA website[§] and product information* for Epilim for the latest information).

Advice to healthcare professionals

- HCPs are reminded that valproate has a high teratogenic potential, with children exposed in-utero having an approximate 11% risk of MCMs and up to 30-40% risk of neurodevelopmental disorders.
- Treatment of women and girls of childbearing potential with valproate must be initiated and supervised by a suitably experienced specialist.
- Use in women of childbearing potential in any indication (epilepsy, bipolar disorder) is contraindicated unless the conditions of a pregnancy prevention programme (known as 'prevent') are fulfilled.
- Further information is available from the HPRA website[§], including a guide for healthcare professionals, as well as within product information* for Epilim.

Reference: 1. Hughes JE, Buckley N, Looney Y, Kirwan G, Curran S, Doherty CP, Mullooly M & Bennett KE (2021) Awareness, knowledge and practice of healthcare professionals following implementation of a pregnancy prevention program for sodium valproate in Ireland: a multi-stakeholder cross sectional study, Expert Opinion on Drug Safety, 20:8, 965-977

* The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is accessible from the HPRA website.

§ http://www.hpra.ie/homepage/medicines/special-topics/valproate-(epilim)