

## Valproate-containing medicines – new EU review initiated

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has, as of March 2017, initiated a new review to examine the use of valproate-containing medicines in the treatment of women and girls who are pregnant or of childbearing potential (WCBP). Valproate-containing medicines are approved nationally in Ireland in various presentations, under the brand name Epilim, to treat epilepsy and bipolar disorder. Valproate-containing medicines are also authorised across Europe in the same indications and, in some countries, are also authorised for migraine, however this remains an unlicensed indication for use in Ireland. The outcome of a previous Europe-wide review of valproate-containing medicines in 2014 was communicated to healthcare professionals in December 2014 via the HPRAs Drug Safety Newsletter (Edition 65) and a Direct Healthcare Professional Communication (DHPC) circulated by the Marketing Authorisation Holder (MAH) following approval by the HPRAs. This 2014 review led to strengthening of restrictions for use of valproate and further characterisation of the risk of birth defects and developmental disorders in the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)).

The current review aims specifically to examine the impact of the risk minimisation measures recommended by the 2014 review. Concerns have been raised in some Member States about how effective these measures have been in practice at increasing awareness of the risk of malformations and developmental problems in babies who are exposed to valproate *in utero*, and ensuring appropriate use of valproate in all its indications (epilepsy, bipolar disorder and, where licensed, prevention of migraine). The PRAC will examine the available evidence and will consult with relevant stakeholder groups, including holding a public hearing to listen directly to the experience of EU patients with these medicines, so that this can be taken into account as part of the Committee's consideration.

Healthcare professionals are reminded that, in May 2015, educational materials were made available by the MAH (following HPRAs approval) as part of the risk minimisation measures developed to inform healthcare professionals and patients about the risks associated with use of valproate by females of childbearing potential and during pregnancy. Updated materials are now available to further support awareness and to facilitate discussion of the risks between healthcare professionals and patients. The availability and a description of these educational materials were communicated in August 2016 via the HPRAs Drug Safety Newsletter (Edition 76). Available materials comprise a valproate patient guide, valproate patient card, booklet for healthcare professionals, and a checklist for prescribers. The materials have been developed with the purpose of supporting safe prescribing and dispensing of valproate-containing medicines, and in particular to ensure that patients and/or carers are informed of the risks. Educational materials are available from the MAH, and on the HPRAs website ([www.hpra.ie](http://www.hpra.ie)). The Health Services Executive (HSE) has also customised documents for use as a local toolkit for prescribers and patients, with these documents accessible from the HSE website.

### Advice to Healthcare Professionals

- Children exposed *in utero* to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases), and/or congenital malformations (in approximately 10% of cases). Available data show that children exposed to valproate *in utero* are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggests that children exposed to valproate *in utero* may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

- Valproate-containing medicines should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated.
- Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of valproate-containing medicines during pregnancy.
- Valproate treatment should be commenced and supervised by a doctor experienced in managing epilepsy or bipolar disorder.
- The benefit and risk of treatment with valproate-containing medicines should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with a valproate-containing medicine plans a pregnancy or if she becomes pregnant.
- Specifically designed educational materials are available for use by healthcare professionals to support safe, fully-informed, prescribing and dispensing of valproate-containing medicines. Patient cards have been developed to be supplied to patients and/or their carers to provide precise and consistent information on the risks. The materials available include a booklet for healthcare professionals, a valproate patient guide, a valproate patient card, and a checklist for prescribers. Educational materials are available from the MAH, and on the HPRA website ([www.hpra.ie](http://www.hpra.ie)).
- The prescriber should ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks. The prescribing checklist is intended to be a tool for the prescribing doctor to ensure that all necessary information has been provided to the patient and/or carer.
- In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

### Key Message

- Valproate-containing medicines are associated with a high teratogenic potential and risk of developmental disorders in infants exposed *in utero* to valproate.
- Educational materials and valproate patient cards are available and should be used by healthcare professionals to support appropriate and safe prescribing/dispensing of valproate-containing medicines, and by patients/carers to increase knowledge of these risks.
- All suspected adverse reactions associated with valproate-containing medicines should be reported to the HPRA via the usual methods ([www.hpra.ie](http://www.hpra.ie)).

*Further information on valproate-containing medicines is available from [www.hpra.ie](http://www.hpra.ie).*

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