

## Teratogenicity of valproate-containing medicines (Epilim<sup>▼</sup>) – Reminder of important restrictions for use in women and girls

Healthcare professionals (HCPs) are aware that valproate-containing medicines (licensed in Ireland as Epilim<sup>▼</sup>) 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<sup>▼</sup> was recently updated to reflect the availability of new scientific information in this regard (see summary of risks on page 4 for further information).

Due to the known teratogenic effects, Epilim<sup>▼</sup> **should not be used** in female children and women of childbearing potential<sup>1</sup> (WCBP), unless other treatments are ineffective or not tolerated. Treatment must be initiated and supervised by a suitably experienced specialist<sup>2</sup>. 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<sup>▼</sup>, as well as the conditions of **prevent** and the necessary actions for HCPs to take in order to minimise the risk of exposure in pregnancy for their patients.

## 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<sup>▼</sup>, 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<sup>3</sup> throughout treatment, pregnancy testing prior to initiation (and as required during treatment), an annual specialist review of the continued appropriateness of treatment with Epilim<sup>▼</sup>, a review of the risks with individual patients, pregnancy planning and pregnancy management.

For **prevent** to be effective, it is essential 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](#), with key messages summarised below for specialists, GPs and pharmacists.



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.

## Key messages for specialists

As a specialist, you have an important role in initiating and supervising the treatment of female children and/or WCBP with Epilim▼ and are responsible for several actions of **prevent**. It is recommended that you consider the need for local systems and procedures to assure the conditions of the licence and **prevent** are consistently implemented for patients in your care.

Should you consider Epilim▼ to be the only suitable treatment option for a patient, the following is a summary of the key actions for which you are responsible:

- ✓ Discuss the risks with the patient (or parent/caregiver/responsible person) and provide a copy of the [patient guide](#).
- ✓ Exclude pregnancy in WCBP (by serum pregnancy test) before the first prescription is issued.
- ✓ Unless there are compelling reasons to indicate that there is no risk of pregnancy, arrange for highly effective contraception for WCBP before the first prescription is issued.
- ✓ Complete the [Annual Risk Acknowledgement Form](#) with your patient (or parent/caregiver/responsible person) on treatment initiation and yearly thereafter, during treatment review.
- ✓ Provide a copy of the signed [Annual Risk Acknowledgement Form](#) to the patient and the patient's GP to facilitate provision of repeat prescriptions.
- ✓ See the patient urgently if referred back in case of unplanned pregnancy or if she wants to plan a pregnancy (see pregnancy section below for further details).
- ✓ For female children, it is particularly important that parents, caregivers or responsible person, as appropriate, are made aware of the need to contact their specialist immediately once menstruation has commenced. The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate in utero. If valproate is the only suitable treatment, the need to use effective contraception and all other conditions of pregnancy prevention programme should be discussed. When menarche is reached, every effort needs to be made to switch patients to an alternative treatment before they reach adulthood.

**Existing patients:** these conditions also apply to patients started on Epilim▼ prior to the implementation of **prevent**, who should by now be identified, and the need for continued treatment assessed. Refer to the [HCP guide](#) for further details on management of existing patients.

## Key messages for general practitioners (GPs)

As a GP, you have a role in supporting implementation of **prevent** in cases where you have a patient that is a female child or WCBP, and to whom you provide repeat Epilim▼ prescriptions. The following is a summary of the key actions for which you are responsible:

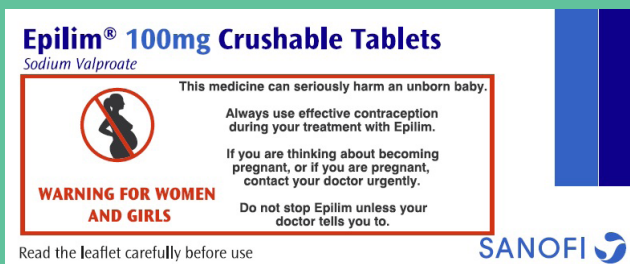
- ✓ Check the patient has a copy of the [patient guide](#) and that you have a copy of an up-to-date signed [Annual Risk Acknowledgement Form](#) each time a repeat prescription is issued
- ✓ Unless there are compelling reasons to indicate that there is no risk of pregnancy, ensure continuous use of highly effective contraception in all WCBP (consider the need for pregnancy testing for any patient not using a highly effective method of contraception or if there is any reason to suggest lack of compliance with contraception).
- ✓ Ensure the patient understands the need to contact you immediately if she suspects there has been a problem with her contraception or she may be pregnant.
- ✓ Ensure she is referred back to her specialist for annual review, and **urgently** in case of unplanned pregnancy (within days) or to plan a pregnancy (see pregnancy section below for further details).

**Existing patients:** refer to the [HCP guide](#) for further information on existing patients, who may have initiated treatment prior to **prevent** and who may not otherwise be under specialist care. Ensure such patients are identified and referred to a specialist, where necessary. The conditions of **prevent** also apply to such patients.

# Key messages for pharmacists

Pharmacists have an important role in dispensing Epilim<sup>▼</sup> to patients, and ensuring this is done in the original packaging, with appropriate guidance, as follows:

- ✓ When dispensing, ensure WCBP have received the [patient guide](#), highlight again the risks in pregnancy and remind the patient of the need for annual specialist review. If a woman of childbearing potential reports that she is not taking highly effective contraception, refer them to their GP (including by contacting the GP if necessary).
- ✓ Dispense valproate in the original package with an outer warning. Dispensing outside of original packaging should be avoided. In situations where this cannot be avoided, always provide a copy of the package leaflet and add a [sticker](#) with the warning to the outer packaging.
- ✓ Epilim<sup>▼</sup> medicines are now available on the market in updated packaging, with reduced pack sizes of 30 units, a removable [patient card](#) attached to outer package and a visual warning on the inner blister. However, legacy stock<sup>4</sup> with variations of older packaging may remain on the market for some time. When legacy stock is dispensed, always provide a copy of the most up-to-date package leaflet (available to download from the HPRA website), together with the [patient card](#) and [valproate warning sticker](#), supplies of which have been issued to all pharmacies by the manufacturer. Further information on this matter was recently communicated in a [letter to pharmacists](#), a copy of which is available on the HPRA website.
- ✓ In case of planned or suspected pregnancy, advise patients not to stop valproate and to immediately contact her specialist for urgent review.



## Pregnancy planning and management

### Patients with bipolar disorder

Valproate (Epilim<sup>▼</sup>) is contraindicated in pregnancy.

If a woman is planning to become pregnant, the prescriber must switch the patient to another treatment, prior to conception and before contraception is discontinued.

If a woman becomes pregnant, treatment with valproate must be discontinued and the patient switched to another treatment.

### Patients with epilepsy

Valproate (Epilim<sup>▼</sup>) is contraindicated in pregnancy unless there is no suitable alternative treatment.

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment, and the patient should be informed not to stop contraception until the switch is achieved and she is no longer taking Epilim<sup>▼</sup>.

If a woman becomes pregnant, an immediate specialist review should be arranged, to allow for alternative treatment options and switching to be considered. If, in **exceptional circumstances**, a pregnant woman must receive valproate for epilepsy, it is recommended to use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day. A prolonged release formulation may be preferable in order to avoid high peak plasma concentrations.

All women with an exposed pregnancy should be referred to an obstetrician.

Refer to the [HCP guide](#) and Summary of Product Characteristics for full details.

4. Batch numbers: expiring late 2020: 7R019, 7R037, 7A221, 7A533, A7816, A7767, 289; expiring early 2021: numbers 8R003, 8A300, 8A514, 303

# Summary of Teratogenic Risks

- Valproate-containing medicines (licensed in Ireland as Epilim<sup>▼</sup>) have a high teratogenic potential. According to studies, children exposed in utero have an up to 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.
- Product information 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 most recent educational materials for Epilim<sup>▼</sup> and the **prevent** programme were distributed in hard copy in May 2018, and again in February 2020. These materials are also available on the [HPRA website](#), and include:

- An [Annual Risk Acknowledgement Form](#) to be used at 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 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 will soon be able to access the patient guide, patient card, Annual Risk Acknowledgement Form and most up to date package leaflets electronically by scanning the QR code which will be printed on the Epilim package leaflet, which will link to the company's Epilim QR code [webpage](#).

*All reports of suspected adverse reactions should be reported to the HPRA via the available methods ([www.hpra.ie](http://www.hpra.ie)).*

## Access to current versions of product information

Healthcare professionals are reminded that SmPCs for all products currently authorised in Ireland are accessible on the HPRA website ([www.hpra.ie](http://www.hpra.ie)). The HPRA advises healthcare professionals not to retain printed versions of Summary of Product Characteristics (SmPC) documents. As these documents are subject to frequent content updates, including changes to safety and dose related information, we recommend that you visit our website as necessary to access the most up-to-date versions.

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