



PLEASE READ
Important Patient Safety Information
Approved by HPRA

Valproate (Epilim ▼): NEW restrictions on use
PREGNANCY PREVENTION PROGRAMME to be put in place.

16 April 2018

Dear Pharmacist,

This letter is sent in agreement with the European Medicines Agency (EMA) and the Health Products Regulatory Authority (HPRA) to inform you of **important new contraindications, strengthened warnings and measures to prevent valproate exposure during pregnancy.**

Summary

- **Valproate should not be used in female children, girls and women of childbearing potential unless other treatments are ineffective or not tolerated.**
- **Children exposed to valproate in utero are at high risk of serious developmental disorders (in up to 30-40% of cases) and of congenital malformations (in approximately 10% of cases).**
- **In pregnancy and in women of childbearing potential new contraindications apply:**
 - **In epilepsy**
 - **valproate is contraindicated in pregnancy unless there is no suitable alternative treatment.**
 - **valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme (described below) are met.**
 - **In bipolar disorder**
 - **valproate is contraindicated in pregnancy.**
 - **valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme (described below) are met.**
- **For women of childbearing potential currently using valproate the treatment may need to be re-evaluated to ensure that the conditions of the pregnancy prevention programme (described below) are met.**

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Key elements of the PREGNANCY PREVENTION PROGRAMME:

The prescriber must ensure that:

- the potential for pregnancy is assessed for all female patients.
- individual circumstances are evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the patient has **understood and acknowledged the risks** of congenital malformations and neurodevelopmental disorders, including the magnitude of these risks for children exposed to valproate in utero.
- the patient understands the need to undergo **pregnancy testing prior to initiation of treatment** and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the **need to use effective contraception**, without interruption during the entire duration of treatment with valproate.
- the patient understands **the need for regular (at least annual) review of treatment by a specialist** experienced in the management of epilepsy or bipolar disorders.
- the patient **understands the need to consult her physician as soon as she is planning a pregnancy** before contraception is discontinued, to ensure enough time for switching to an alternative treatment prior to conception.
- the patient understands **the need to urgently consult her physician in case of pregnancy**.
- the patient has **received and understood the patient guide**.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use and has signed the **Annual Risk Acknowledgement Form** that should be recorded in her Patient Medical Records.

These conditions also concern women who are not sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The Summary of Product Characteristics and Patient Information Leaflet of all valproate-containing products will be updated accordingly.

It is recommended that pregnant women taking antiepileptic drugs in general, and valproate in particular, are enrolled in the Irish Epilepsy and Pregnancy Register (www.epilepsyandpregnancyregister.ie).

More **detailed instructions related to the following topics** are **provided in the Annex** of this letter:

- a. the use of valproate in female children.
- b. the need to rule out pregnancy before valproate initiation.
- c. the use of effective contraception.
- d. the annual treatment review by a specialist.
- e. the use of the annual risk acknowledgement form (at treatment initiation and during treatment review, at least annually).
- f. what to do with valproate treatment at the time of pregnancy planning and during pregnancy
- g. specific actions to be taken by the pharmacist such as provision of the patient card.

Educational Materials

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, **revised** Educational Materials have been produced which provide information on the risks of valproate and the conditions for use. These include:

- a patient card (the packaging will be updated to include this on the outer carton) – to be provided to all female patients when dispensing valproate to them
- a patient guide
- a healthcare professional guide
- an annual risk acknowledgment form – to be used by the specialists at time of treatment initiation and during each annual review of valproate treatment by the specialist. The prescriber should document that the patient has understood the risks at every annual visit. This should be signed by the patient and prescriber and recorded in her Patient Medical Record.

Hardcopies of the patient guide, the healthcare professional guide and the acknowledgement of risk form will be distributed shortly, the materials will also be available electronically on www.hpra.ie (enter 'Epilim' or 'valproate' under 'Find a Medicine' and click 'EdM' under the 'Documents' column) and www.sanofi.ie.

Additionally, a pharmacy poster and shelf barker will also be sent to each pharmacy. You are asked to display the poster in the dispensary as a visual reminder to pharmacy staff of the pregnancy prevention programme and the warnings related to the use of valproate and the need to counsel female patients on the risks. Warning stickers will also be provided to pharmacies for use where Epilim is dispensed outside of the original packaging.

Should additional hardcopy versions of any of the materials be required, these can be ordered by contacting Sanofi Medical Information on **Tel: (01) 403 5600 or e-mail: IMedinfo@sanofi.com**.

PHARMACISTS are asked to take the following IMPORTANT ACTIONS when dispensing valproate to female patients:

- 1. Provide a Valproate Patient Card every time you dispense a valproate preparation and ensure that the patient understands its content.**
- 2. Check that their prescriber has discussed the risks of in utero exposure with them and reinforce the need for effective contraception. Remind the patient of the need for annual specialist review.**
- 3. Advise the patients not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.**
- 4. Ask if they have received a Valproate Patient Guide and provide a copy if they have not received this or no longer have it in their possession.**
- 5. Dispense valproate in the original package with the outer carton warning text and symbol. Dispensing outside of original packaging (i.e broken bulk dispensing) should be avoided. In the situations where this cannot be avoided, always provide a copy of the package leaflet, patient card and add a warning sticker to the bag or box into which the blisters have been placed.**
- 6. Please ensure you cascade this important information to all dispensary staff and display the valproate poster and shelf barker in your dispensary as a visible reminder to staff of the pregnancy prevention programme, the warnings related to the use of valproate and the need to counsel female patients on the risks. The warning stickers along with hardcopies of the aforementioned materials will be sent to all pharmacies shortly.**

Background on the safety concern

In 2014 the warnings and restrictions on the use of valproate medicines in women and girls were strengthened, to minimise the risk of malformations and developmental problems in babies exposed to valproate in the womb. EMA's safety experts, the Pharmacovigilance Risk Assessment Committee (PRAC) have now reviewed the impact of these measures following concerns that the measures were not sufficiently effective in increasing awareness and reducing valproate use during pregnancy. The PRAC found these concerns to be well founded and have therefore introduced new measures.

Risk of abnormal pregnancy outcomes

Valproate is associated with a dose-dependent risk of abnormal pregnancy outcomes, whether taken alone or in combination with other medicines. Data suggest that when valproate is taken for epilepsy with other medicines, the risk of abnormal pregnancy outcomes is even greater than when valproate is taken alone. When valproate is taken alone:

- The risk of congenital malformations for children exposed in utero is approximately 10%, and studies in preschool children exposed in utero show that in up to 30-40%, early development such as talking, and walking is delayed and they have low intellectual abilities, poor language skills and memory problems. ^{1,2,3,4}
- Intelligence quotient (IQ) measured in a study of 6 year old children with a history of valproate exposure in utero was on average 7-10 points lower than children exposed to other antiepileptics.⁵
- 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 suggest that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD) ^{6,7,8}

Call for reporting

Valproate (Epilim) is subject to additional monitoring.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2;

Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

Adverse events arising from the use of medicines manufactured by Sanofi may also be reported to the **Sanofi IE Pharmacovigilance** department at: Sanofi, 18 Riverwalk, Citywest Business Campus, Dublin 24.

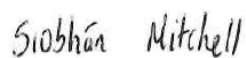
Tel: +353 1 403 5600, Fax: +353 1 403 5687, Email: IEPharmacovigilance@sanofi.com.

Company contact point

Further information is available on request from the Marketing Authorization Holder contactable at the address indicated on the packaging, in the Summary of Product Characteristics or Patient Leaflet, by calling 01-4035600 or e-mailing JEmedinfo@sanofi.com.

Thank you for your co-operation in following these requirements. This will help ensure appropriate use of valproate in this patient group and minimise these significant risks.

Yours faithfully



Dr Siobhan Mitchell

Medical Director, Sanofi Ireland

Annex

Further details on the pregnancy prevention programme

The following information should be read in conjunction with the conditions of the pregnancy prevention programme which are described in the letter above.

a. Female children

- Valproate should not be prescribed to female children unless there is no suitable alternative treatment.
- The prescribers must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- 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*.
- In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the need to use effective contraception and all other conditions of pregnancy prevention programme should be discussed. Efforts should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

b. Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of child bearing potential, unless they have a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

c. Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably 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, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

d. Annual treatment reviews by a specialist

The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss the annual risk acknowledgement form, at initiation and during each annual review and ensure that the patient has understood its content.

e. Pregnancy planning

Epilepsy

For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Before contraception is discontinued, every effort should be made to switch to appropriate alternative treatment prior to conception. If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

Bipolar disorder

For the indication bipolar disorder, if a woman is planning to become pregnant a specialist experienced in the management of bipolar disorder must be consulted and, before contraception is discontinued, treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception.

f. In case of pregnancy

Bipolar disorder

Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy.

Epilepsy

Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment.

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, 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. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in teratology for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

g. Pharmacists must ensure that:

- The patient card is provided every time valproate is dispensed and that the patient understands its content.
- They reinforce the safety messages, including the need for effective contraception.
- Patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

- Valproate should be dispensed in its original package with the outer carton warning text and symbol. Dispensing outside of original packaging (i.e. broken bulk dispensing) should be avoided. In the situations where this cannot be avoided, always provide a copy of the package leaflet, patient card and add a sticker with the warning to the outer bag or box into which the blisters have been placed (these stickers will be provided to pharmacies).

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- ¹ Meador K, Reynolds MW, Crean S, *et al.* Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res* 2008;81(1):1-13
 - ² Meador KJ, Penovich P, Baker GA, *et al.* Antiepileptic drug use in women of childbearing age. *Epilepsy Behav* 2009;15(3):339-43.
 - ³ Bromley RL, Mawer G, Clayton-Smith J, *et al.* Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology* 2008;71(23):1923-4.
 - ⁴ Cummings C, Stewart M, Stevenson M, *et al.* Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011 July;96(7):643-7
 - ⁵ Meador KJ, Baker GA, Browning N, *et al.* Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013;12(3):244-52.
 - ⁶ Christensen J, Grønberg TK, Sørensen MJ *et al.* Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA*. 2013; 309(16):1696-703.
 - ⁷ Cohen MJ, Meador KJ, Browning N, *et al.* Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6years. *Epilepsy Behav* 2013;29(2):308-15.
 - ⁸ Cohen M.J *et al.* Fetal Antiepileptic Drug Exposure: Motor, Adaptive and Emotional/Behavioural Functioning at age 3 years. *Epilepsy Behav*. 2011; 22(2):240-246