**PLEASE READ**
**Important Patient Safety Information**
**Approved by HPRA**

# Valproate (Epilim▼):
# PREGNANCY PREVENTION PROGRAMME
# Update of educational materials
# Healthcare Professional Guide and Patient Guide

**July 2020**

**Dear Healthcare professional,**

This letter is to inform you of **updates to the valproate Healthcare Professional and Patient Guides** following changes in the prescribing information approved by the Health Products Regulatory Authority.

Information related to the risks of abnormal pregnancy outcomes in children exposed to valproate in utero, with new information on the risk of hearing impairment or deafness and updates related to the risk of ADHD have been included in these guides. Full details of the updated sections of the guides are outlined in the attached Annex – Valproate Educational Materials Update 2020.

Electronic versions of these updated materials are available immediately on www.hpra.ie (enter 'Epilim' or 'valproate' in the 'Find a medicine' search box and click on 'EdM' next to any of the medicines that appear).

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

Healthcare professionals should ensure that their patients are provided with the most up-to-date version of the Patient Guide.



Sanofi-Aventis Ireland Limited T/A SANOFI, Citywest Business Campus, Dublin 24, Ireland - Tel: +353 1. 40 35 600 - Fax: +353 1 40 35 601
Registered in Dublin, Ireland No. 166500 Directors: M. Dempsey, FX. Duhalde (French)

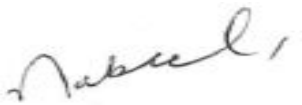
**Call for reporting**

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, Website: www.hpra.

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

Yours faithfully



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Dr. Nabeel Shafaat
Established Products Medical Lead
Sanofi UK & Ireland

## Annex - Valproate Educational Materials update 2020

### GUIDE FOR HEALTHCARE PROFESSIONALS

### 4. Information on congenital malformations and on developmental disorders

Valproate contains valproic acid, an active ingredient with known teratogenic effects which may result in congenital malformations.

### 1. Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) have shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% confidence interval: 8.16–13.29%). This represents a greater risk of major malformations than for the general population, for whom the risk is equal to about 2–3%[1]. Available data show that the risk is dose-dependent.
The risk is greatest at higher doses. A threshold dose below which no risk exists cannot be established based on available data.

The most common types of malformations 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. *In utero* exposure to valproate may also result in unilateral or bilateral hearing impairment or deafness, that may not be reversible[2].

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.

### 2. Developmental disorders

Exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk 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 regardless of when during the pregnancy exposure occurs cannot be excluded.

Studies~~[3-6]~~[2] ~~[5]~~ in preschool children show that up to 30–40% of children with a history of valproate exposure *in utero* experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6 years old) with a history of valproate exposure *in utero* was on average 7–10 points lower than children exposed to other antiepileptic drugs~~[7]~~[6]. Although the role of confounding factors cannot be ruled out, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data from a population based study show that children with a history of valproate exposure *in utero* are at increased risk of autistic spectrum disorder (~~an~~ approximately ~~three~~3-fold ~~increased risk~~) and childhood autism (~~an~~approximately ~~five~~5-fold ~~increased risk~~) compared ~~with the general study~~to the unexposed population in the study[~~8~~7].

~~Limited~~ Available data from another population based study show ~~suggest~~ that children with a history of valproate exposure *in utero* ~~may be more likely to~~ are at increased risk of developing ~~symptoms of~~ attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study[9].~~[8]~~

**GUIDE FOR PATIENTS**

**Birth defects**

**Taking valproate (Epilim) during pregnancy can cause serious birth defects.**
In women who take valproate while pregnant:
• Around 10 babies in every 100 will have a birth defect.
In women in the general population:
• 2 to 3 babies in every 100 will have a birth defect.

**What type of birth defects can happen?**
• Spina bifida – where the bones of the spine do not develop properly.
• Face and skull malformations – including 'cleft lip' and 'cleft palate'. This is where the upper lip or bones in the face are split.
• Malformations of the limbs, heart, kidney, urinary tract and sexual organs.
• Hearing problems or deafness.

**Development and learning problems**

**Taking valproate (Epilim) while pregnant could affect your child's development as they grow up.**
In women who take valproate while pregnant:
• Up to 30–40 children in every 100 may have problems with development.
The following effects on development are known:
• Being late in learning to walk and talk.
• Lower intelligence than other children of the same age.
• Poor speech and language skills.
• Memory problems.

Children of mothers who take valproate in pregnancy are more likely to have autism or autistic ~~autism~~ spectrum problems and are at increased risk of ~~. The children may be more likely to have signs of~~developing Attention Deficit Hyperactivity Disorder (ADHD).