sanofi

PLEASE READ

IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

15th September 2023

Valproate (Epilim▼) – ongoing review of potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months prior to conception.

Dear Healthcare professional,

Sanofi-Aventis Ireland Ltd. T/A Sanofi in agreement with the Health Products Regulatory Authority (HPRA) would like to inform you of the following:

Summary

- **The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) is currently evaluating the results of a retrospective observational study on electronic medical records in Denmark, Norway and Sweden (EUPAS32401) to assess the risk of neurodevelopment disorders (NDDs), including autism spectrum disorders, as well as congenital abnormalities in children fathered by men taking valproate-containing medicines in comparison to those fathered by men treated with lamotrigine / levetiracetam.**
- **Initial results from this study may indicate an increased risk of NDDs in children of men treated with valproate in the three months prior to conception, compared to those treated with lamotrigine or levetiracetam. However, the PRAC has identified important limitations with the data from the study. In addition, errors in the Norwegian dataset were identified after submission of the study results. The initial findings are therefore subject to change.**
- **The PRAC has requested the pharmaceutical companies involved to provide re-analyses of corrected data, as well as additional information and additional analyses to address the study limitations, as soon as possible.**
- **Patients should be advised that they should not stop taking valproate without first consulting their healthcare professional and also to talk to their healthcare professional if they have questions or concerns.**
- **This update is provided to inform healthcare professionals of the ongoing EMA review. Further updates on this review as well as any recommendations that may arise will be communicated to patients and healthcare professionals, as appropriate.**

Background on the safety concern

Valproate-containing medicines are indicated for the treatment of epilepsy and bipolar disorder.

In 2018, following an EMA review which resulted in strengthened warnings and measures to prevent valproate exposure via maternal use during pregnancy, pharmaceutical companies which market these medicines were required to conduct a study to investigate the association between paternal exposure to valproate and the risk of NDDs, including autism spectrum disorders, as well as congenital abnormalities in offspring **(EUPAS32401)**.

This retrospective observational study was conducted using data from multiple registry databases in Denmark, Sweden and Norway.

The initial analyses of the data suggest an increased risk of NDDs in children born to men treated with valproate in the three months prior to conception, compared to those born to men treated with lamotrigine or levetiracetam. However, after submitting the study results, the companies who conducted the study informed the PRAC of errors in the Norwegian dataset relevant to the analysis of risk of NDDs, the impact of which is not yet known. The PRAC has also identified important limitations of the current data, including questions about the definition of NDDs in the study as well as the specific types of epilepsy the fathers had. These findings are therefore subject to change.

The PRAC has requested companies to provide corrected analyses and additional analyses to address study limitations as soon as possible. The PRAC will review the required data as they become available and make an EU-wide recommendation.

With respect to congenital malformations, the study did not suggest an increased risk in children fathered by men treated with valproate in the three months preceding conception in comparison to those fathered by men treated with lamotrigine / levetiracetam.

This update is provided to inform healthcare professionals of the ongoing EMA review.

Patients should be advised that they should not stop taking valproate without first consulting their healthcare professional and to talk to their healthcare professional if they have questions or concerns.

Further updates on this review as well as any recommendations that may arise will be communicated to patients and healthcare professionals, as appropriate.

Healthcare professionals are also reminded that product information already includes advice that valproate administration may impair fertility in men. The frequency of male infertility with valproate is rare (≥1/10,000 to ≤1/1,000). Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited number of case reports suggest that a strong dose reduction may improve fertility function. However, in some other cases, the reversibility of male infertility was unknown.

The ongoing evaluation of the results of the study on paternal exposure to valproate does not affect the important contraindications, warnings, restrictions and risk minimisation measures in place to prevent valproate exposure via maternal use during pregnancy (see http://www.hpra.ie/homepage/medicines/special-topics/valproate-(epilim)

for more information on the PREVENT pregnancy prevention programme).

Call for reporting

This medicinal product is subject to additional monitoring.

Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

Adverse events should also be reported to Sanofi Ireland Ltd. Tel: 01 403 5600. Alternatively, send via email to IEPharmacovigilance@sanofi.com

Company contact point

Should you have any questions or require additional information, please contact Medical Information Department at IEmedinfo@sanofi.com or by phone on 01 403 5600.

Yours sincerely,

R Grundy

Rod Grundy

Senior Medical Advisor-Foundation Portfolio

General Medicines

UKIE

Annexes

Information published on EMA website on ongoing review of data on paternal exposure to valproate:

https://www.ema.europa.eu/en/news/ema-review-data-paternal-exposure-valproate