# EMA review of data on paternal exposure to valproate

23/08/2023 | Circular Number P07/2023

## Information on valproate

- Valproate medicines are used to treat epilepsy and bipolar disorder. In some EU Member States, they are also authorised to prevent migraine headaches.

- The active ingredient in these medicines may be valproic acid, magnesium valproate, sodium valproate, valproate semisodium or valpromide. Valproate medicines have been authorised via national procedures in all EU Member States and in Norway and Iceland. They are marketed under several brand names.

The following products are authorised via national procedure.

| Active Ingredients | Product Name | Pharmaceutical Form | Classif-cation | Authorisation Number | MAH/license holder |
|---|---|---|---|---|---|
| Valproate Sodium 400mg | Epilim | Intravenous powder & solvent for solution for injection or infusion | POM | MA1359/01903 | Sanofi S.R.L. |
| Valproate Sodium 200mg/5ml | Epilim Liquid | Oral Solution | POM | MA1359/01904 | Sanofi S.R.L. |
| Valproate Sodium 200mg | Epilim Chrono | Prolonged Release Tablet | POM | MA1359/01901 | Sanofi S.R.L. |
| Valproate Sodium 500mg | Epilim Chrono | Prolonged Release Tablet | POM | MA1359/01902 | Sanofi S.R.L. |
| Sodium Valproate 400mg/4ml | Sodium Valproate Aguettant | Solution for Injection | POM | AA036/00701 | Laboratoire Aguettant |

## Information from the EMA about the safety concern

- EMA's Pharmacovigilance Risk Assessment Committee (PRAC) is reviewing data on the potential risk of neurodevelopmental disorders (NDDs) in children conceived by fathers taking valproate medicines.

- The review is focussing on data from a retrospective observational study conducted by companies as an obligation following a previous review of valproate use during pregnancy.
- This retrospective observational study compared the risk of NDDs (including autism spectrum disorder) in children born to men taking valproate with the risk in children born to men taking lamotrigine or levetiracetam (other treatments for epilepsy). It was carried out using multiple registry databases in Denmark, Norway and Sweden.
- Initial results of the study may indicate an increased risk of NDDs in children born to men taking valproate in the three months before conception. However, the PRAC has identified important limitations with the data from the study.
- In particular, the PRAC had questions about the definition of NDDs used in the study and the specific type of epilepsy the patients had. The latter is important because valproate may be prescribed more often for some types of epilepsy which are associated with NDDs.
- In addition, after submitting the study results, the companies informed the PRAC about errors in the Norwegian database; the impact of these errors is not yet known.
- The PRAC has therefore requested companies to provide analyses of corrected data and additional information as soon as possible to address the limitations.
- The PRAC will review the required data as they become available and make an EU-wide recommendation. While awaiting the outcome of the PRAC's evaluation, some Member States have implemented interim national recommendations.
- Male patients being treated with valproate should not stop taking their medicine without talking to their doctor, as their epilepsy or bipolar disorder could become worse. Sudden discontinuation of treatment for epilepsy could trigger seizures. Patients who have any questions about their treatment should speak to their healthcare professional.
- Previous recommendations to avoid exposure to valproate medicines in women during pregnancy due to the risk of congenital malformations (birth defects) and neurodevelopmental disorders remain in place.

**Reporting Adverse Drug Reactions**

Healthcare professionals and patients are encouraged to maintain vigilance with valproate containing medicines. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form and sending it to: Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 **or** online to http://www.medicinesauthority.gov.mt/adrportal or to the marketing authorisation holder or their local representatives.

**Post-Licensing Directorate**

**Medicines Authority**

***Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.***

**Feedback Form**

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health.

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required).

**Feedback:**

We thank you for your interest and look forward to hearing your opinion.

Postage will be paid
by the Licensee

No postage stamp
necessary if posted
in Malta and Gozo

BUSINESS REPLY SERVICE

Licence no. 656

Pharmacovigilance Section

Post-Licensing Directorate

Medicines Authority

Sir Temi Żammit Buildings

Malta Life Sciences Park

San Ġwann SĠN 3000