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Precautionary measures to address potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines

On 24 January 2024, the CMDh[1] endorsed precautionary measures recommended by EMA's safety committee (PRAC) for the treatment of male patients with valproate medicines. These measures are to address a potential increased risk of neurodevelopmental disorders in children born to men treated with valproate during the 3 months before conception. Valproate medicines are used to treat epilepsy, bipolar disorders and, in some EU countries, migraine.

It is recommended that valproate treatment in male patients is started and supervised by a specialist in the management of epilepsy, bipolar disorder or migraine.

Doctors should inform male patients who are taking valproate about the possible risk and discuss the need to consider effective contraception, for both the patient and their female partner. Valproate treatment of male patients should be reviewed regularly to consider whether it remains the most suitable treatment, particularly when the patient is planning to conceive a child.

In reaching its conclusion, the PRAC reviewed data from a retrospective observational study carried out by companies that market valproate as an obligation following a previous review of valproate use during pregnancy. The Committee also considered data from other sources, including non-clinical (laboratory) studies and scientific literature, and consulted patients and clinical experts.

The retrospective observational study used data from multiple registry databases in Denmark, Norway and Sweden and focused on birth outcomes in children born to men who were taking valproate or taking lamotrigine or levetiracetam (other medicines to treat conditions similar to those treated with valproate) around the time of conception.

The results of the study suggest there may be an increased risk of neurodevelopmental disorders in children born to men taking valproate in the 3 months before conception. Neurodevelopmental disorders are problems with development that begin in early childhood, such as autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders and movement disorders.

The data showed that around 5 out of 100 children had a neurodevelopmental disorder when born to fathers treated with valproate compared with around 3 out of 100 when born to fathers treated with

[1] The CMDh is a medicines regulatory body representing the European Union (EU) Member States, as well as Iceland, Liechtenstein and Norway.

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lamotrigine or levetiracetam. The study did not investigate the risk in children born to men who stopped using valproate more than 3 months before conception.

The possible risk in children born to men treated with valproate in the 3 months before conception is lower than the previously confirmed risk in children born to women treated with valproate during pregnancy. It is estimated that up to 30 to 40 out of 100 preschool children whose mothers took valproate during pregnancy may have problems with early childhood development, such as being slow to walk and talk, being intellectually less able than other children, and having difficulty with language and memory.

The study data on male patients had limitations, including differences between the groups in the conditions for which the medicines were used and in follow-up times. The PRAC could therefore not establish whether the increased occurrence of these disorders suggested by the study was due to valproate use. In addition, the study was not large enough to identify which types of neurodevelopmental disorders children could be at increased risk of developing. Nonetheless, the Committee considered precautionary measures were warranted to inform patients and healthcare professionals.

The potential risk of neurodevelopmental disorders and the precautionary measures will be reflected in updates to the product information and educational material for valproate medicines.

Following the adoption of the PRAC recommendations by the CMDh, these measures will now be implemented in all Member States where valproate-containing medicines are authorised.

Information for male patients

- New information suggests that there may be a higher risk of neurodevelopmental disorders (problems with development that begin in early childhood) in children born to fathers treated with valproate in the 3 months before conception compared with those born to fathers who used lamotrigine or levetiracetam.
- As the study has limitations, it is not possible to confirm that this increased risk is caused by valproate.
- It is recommended that your valproate treatment is started and supervised by a specialist experienced in managing your type of disease.
- Your doctor will regularly review your valproate treatment to consider whether valproate remains the most suitable treatment for you and to discuss the possibility of other treatments to treat your disease, depending on your situation.
- As a precautionary measure your doctor will discuss with you:
  - the potential risk to children born to fathers taking valproate;
  - the need to consider effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment;
  - the need to consult them if you are planning to conceive a child and before stopping contraception;
  - why you should not donate sperm when taking valproate and for 3 months after stopping valproate.

- If your female partner becomes pregnant and you were using valproate in the 3 months leading up to conception, talk to your doctor if you or your partner have questions.
- Do not stop your treatment without consulting your doctor. If you stop treatment your symptoms may get worse.
- Your doctor will give you a patient guide to read. You will also receive a patient card with your medicine, reminding you of the potential risks of using valproate.

Information for healthcare professionals

- It is recommended that valproate treatment in male patients is initiated and supervised by a specialist in the management of epilepsy, bipolar disorder or migraine.
- Healthcare professionals should:
  - inform male patients currently being treated with valproate of the potential risk of neurodevelopmental disorders and consider whether valproate remains the most appropriate treatment;
  - discuss with male patients the need to consider effective contraception, including for their female partner, while using valproate and for at least 3 months after stopping treatment;
  - inform male patients about the need for regular reviews by their doctor to assess if valproate remains the most appropriate treatment for the patient and discuss suitable treatment alternatives with the patient. This is particularly important if the male patient is planning to conceive a child and, in this case, before discontinuing contraception;
  - advise male patients not to donate sperm during treatment and for at least 3 months after treatment discontinuation;
  - provide male patients with the new patient guide for male patients and alert them to the patient card attached to, or included in, their medicine's packaging.
- These precautionary measures are based on a PRAC review of data from a retrospective observational study (EUPAS34201). The results suggest an increased risk of neurodevelopmental disorders in children born to men treated with valproate in the 3 months prior to conception compared with the risk in those born to men treated with lamotrigine or levetiracetam.
- Meta-analysis of data from 3 Nordic countries resulted in a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07) for neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception compared with lamotrigine or levetiracetam. The adjusted cumulative risk of neurodevelopmental disorders was estimated to be around 5% in the valproate group versus around 3% in the lamotrigine and levetiracetam group. No difference in the risk of congenital malformations was seen between the two groups.
- The study did not evaluate the risk of neurodevelopmental disorders in children born to fathers who stopped using valproate more than 3 months before conception.
- Previous recommendations to avoid exposure to valproate medicines in women during pregnancy due to the risk of congenital malformations and neurodevelopmental disorders remain in place.

A direct healthcare professional communication (DHPC) will be sent in due course to healthcare professionals prescribing, dispensing or administering the medicine. The DHPC will also be published on a dedicated page on the EMA website.

More about the medicine

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 including: Absenor, Convival Chrono, Convulex, Delepsine, Depakin, Depakine, Depakote, Depamide, Deprakine, Diplexil, Epilim, Episenta, Epival Cr, Ergenyl, Hexaquin, Kentlim, Micropakine L.P., Orfiril, Valpal, Valpro and Valprolek.

More about the procedure

The review of valproate was initiated on 13 March 2023 following submission by the marketing authorisation holders of results from a post-authorisation safety study (EUPAS34201) in accordance with Article 107p of Directive 2001/83/EC. This study was an obligation arising from a previous review of the use of valproate during pregnancy.

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. The PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which has adopted its position. The CMDh is a body representing EU Member States as well as Iceland, Liechtenstein and Norway. It is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by consensus, the measures will be directly implemented by the Member States where these medicines are authorised.