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

European Medicines Agency (EMA) announces that the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh) 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 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 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 professional 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.

Please refer to the following website in EMA for details:
http://www.ema.europa.eu/en/news/precautionary-measures-address-potential-risk-neurodevelopmental-disorders-children-born-men-treated-valproate-medicines

In Hong Kong, there are 9 registered pharmaceutical products containing valproate. All products are prescription-only medicines. So far, the Department of Health (DH) has received 15 cases of adverse drug reaction related to valproate, but these cases were not related to neurodevelopmental disorders in children after paternal exposure to valproate.

Related news was previously issued by Singpaore's Health Science Authority (HSA), the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA), and was posted on the Drug Office website since 22 Mar 2023, with the latest update posted on 24 Jan 2024. Letters to inform local healthcare professionals were issued by the DH on 22 Mar 2023.

In light of the above EMA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

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