31/05/2018
EMA/375438/2018

New measures to avoid valproate exposure in pregnancy endorsed

Member State representatives agree new restrictions and pregnancy prevention programme

On 21 March 2018 the CMDh[1] endorsed new measures to avoid exposure of babies to valproate medicines in the womb, because exposed babies are at high risk of malformations and developmental problems.

Valproate-containing medicines have been approved nationally in the EU to treat epilepsy and bipolar disorder and in some countries for prevention of migraine. The new measures include a ban on the use of such medicines for migraine or bipolar disorder during pregnancy, and a ban on treating epilepsy during pregnancy unless there is no other effective treatment available.

Further, the medicines must not be used in any woman or girl able to have children unless the conditions of a new pregnancy prevention programme are met. The programme is designed to ensure that patients are made fully aware of the risks and the need to avoid becoming pregnant.

A visual warning of the pregnancy risks (in the form of boxed text with other possible elements such as a warning symbol) must also be placed on the packaging of the medicines and warnings be included on patient cards attached to the box and supplied with the medicine each time it is dispensed.

The CMDh agreed with EMA's Pharmacovigilance Risk Assessment Committee (PRAC), which carried out a review and recommended the new measures, that despite previous recommendations aimed at better informing patients of the risks with these medicines, women were still not always receiving the right information in a timely manner. The new measures endorsed by CMDh therefore strengthen previous restrictions on valproate use and requirements to inform women of the risk.

Companies marketing these medicines are also required to carry out additional studies on the nature and extent of the risks and to monitor valproate use and the long-term effects from affected pregnancies.

Because the CMDh position was agreed by majority vote it was sent to the European Commission, which issued a final legally binding decision valid across the EU.

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

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Information for patients and healthcare professionals

- Medicines containing valproate have been available in EU countries for many years to treat epilepsy, bipolar disorder and in some countries migraine. It is known that if taken in pregnancy they can cause malformations in the baby and developmental disorders after birth.
- Although steps had been taken previously to better inform women about these risks and discourage use of valproate in girls and women unless there was no alternative, the evidence shows that this information is still not getting to patients.
- Valproate medicines are now therefore contraindicated, i.e. must not be used, in girls and women able to have children unless the terms of a special **pregnancy prevention programme** are followed. These include:
  - an *assessment* of each patient's potential for becoming pregnant,
  - *pregnancy tests* before starting and during treatment as needed,
  - *counselling* about the risks of valproate treatment and the need for *effective contraception* throughout treatment,
  - a *review of ongoing treatment* by a specialist at least annually,
  - introduction of a new *risk acknowledgement form* that patients and prescribers will go through at each such annual review to confirm that appropriate advice has been given and understood.
- As before, valproate treatment should never be started unless alternative treatments are not suitable, including in young girls below the age of puberty.
- In **pregnancy**, valproate is contraindicated and an alternative treatment should be decided on, with appropriate specialist consultation, for women planning pregnancy; however, there may be a small number of women with epilepsy for whom there is no suitable alternative treatment to valproate and who should be appropriately supported and counselled.
- There will be changes to the **product information** (package leaflet for patients and SmPC for healthcare professionals) to reflect these new conditions and also to the packaging of the medicine, including a **visual warning** in the form of boxed text which may be accompanied by other elements such as a symbol. The medicines authorities in the individual countries will approve appropriate details of the visual warning for their national situation.
- **Educational materials** in the form of guides for patients and doctors will also be updated to reflect the current situation and provide age-appropriate advice. In addition, there will be a **patient alert card** attached to the packaging so that pharmacists can go through it with the patient when the medicine is dispensed.
- It is important that patients discuss any concerns about their medication with an appropriate healthcare professional. **Women and girls who have been prescribed valproate should not stop taking their medicine without consulting their doctor as doing so could result in harm to themselves or to an unborn child.**
- Healthcare professionals will receive further information at national level in due course as the recommendations are implemented.

The companies that market valproate must carry out **further studies** to characterise the nature and extent of the risks posed by valproate and monitor ongoing valproate use and the long-term effects from affected pregnancies. This will include surveys of healthcare professionals and patients to assess

the reach and effectiveness of the new measures, and use of data from existing registries to further characterise the malformations known as foetal anticonvulsant syndrome in children whose mothers took valproate in pregnancy and how this compares to other anti-epileptic medicines. It also includes a retrospective observational study to look at any association between exposure to valproate in men and the risk of malformations and developmental disorders including autism in offspring, and an observational study to evaluate and identify the best practice for stopping and switching of valproate treatment.

In addition, all companies marketing such medicines will need to have in place a **risk management plan** which details the measures taken to ensure that a medicine is used as safely as possible.

Basis for the recommendations

The measures are based on a review of available scientific evidence, including drug utilisation studies and clinical and laboratory evidence of the effects of the medicine. During the review, the PRAC also consulted very widely with healthcare professionals and with patients, including women and their children who have been affected by valproate use during pregnancy, through written submissions, expert meetings, meetings with stakeholders (including healthcare professionals, patients organisations, patients and their families), and via a public hearing.

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, Depamag, Depamide, Deprakine, Diplexil, Dipromal, Epilim, Episenta, Epival, Ergenyl, Espa-Valept, Hexaquin, Kentlim, Leptilan, Micropakine L.P., Orfiril, Petilin, Valepil, Valhel PR, Valpal, Valpro and Valprolek.

More about the procedure

The review of valproate medicines was initiated on 9 March 2017 at the request of the French medicines regulator ANSM, under Article 31 of Directive 2001/83/EC.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were sent to Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a 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 majority vote, it was sent to the European Commission, which issued an EU-wide legally binding decision on 31/05/2018.