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附件：歐洲EMA及英國MHRA警訊各1份（A21020000I_1131403611_doc2_Attach1.pdf、A21020000I_1131403611_doc2_Attach2.pdf）

主旨：有關本署擬進行含valproate 類成分藥品之臨床效益及風險再評估一案，詳如說明段，請查照。

說明：

一、歐洲藥品管理局（歐洲EMA）於113年1月12日及英國醫藥管理局（英國MHRA）於113年1月22日發布安全性警訊，說明男性於女性受孕前三個月使用含valproate成分藥品可能增加其孩童神經發育障礙（neurodevelopmental disorders）及可能使男性生育能力受損等風險（詳如附件）。本署為確保民眾用藥安全，故啟動旨揭成分藥品之臨床效益及風險再評估。

二、為進行含valproate 類成分藥品之臨床效益及風險再評估，貴會倘有相關意見或下列相關研究文獻資料，請於113年8月31日前檢送至本署，逾期未提具資料者，視同無意見：

(一)請就含valproate 類成分藥品之臨床使用、臨床效益及

安全性提供相關意見。

(二)臨床上是否有疑似男性於女性受孕前三個月使用旨揭成分藥品導致孩童神經發育障礙或使男性生育能力受損之案例或國內相關統計數據？

(三)是否同意於「用法及用量：特殊族群用法用量」處加刊「男性：建議應由專科醫師開立。」？

(四)是否同意於「警語及注意事項」及「特殊族群注意事項」處加刊「男性於女性受孕前三個月內使用valproate，相對於使用lamotrigine 或levetiracetam之父親，其孩童發生神經發育障礙風險增加。男性使用valproate 亦可能使生育能力受損。」？

(五)其他意見或建議。

正本：中華民國醫師公會全國聯合會、中華民國藥師公會全國聯合會、社團法人臺灣臨床藥學會、臺灣醫學會、台灣內科醫學會、台灣婦產科醫學會、社團法人台灣急診醫學會、台灣家庭醫學醫學會、中華民國神經外科醫學會、台灣神經學學會、台灣兒科醫學會、台灣新生兒科醫學會、台灣外科醫學會、台灣生殖醫學會、中華民國重症醫學會、中華民國急救加護醫學會、台灣癲癇醫學會、台灣頭痛學會、台灣小兒神經醫學會、台灣精神醫學會

副本：全國藥物不良反應通報中心、財團法人醫藥品查驗中心、衛生福利部中央健康保險署 電子公文交換章 2024/07/30 09:38:59

← News

Potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines: PRAC recommends precautionary measures

12 January 2024

EMA's safety committee (PRAC) is recommending precautionary measures for the treatment of male patients with valproate medicines.

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EMA's safety committee (PRAC) is recommending precautionary measures 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.

The PRAC recommends 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.

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 will now be sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt 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.

Related content

- Valproate and related substances - referral
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 January 2023

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Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): new safety and educational materials to support regulatory measures in men and women under 55 years of age

New safety and educational materials have been introduced for men and women and healthcare professionals to reduce the harms from valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the risk of impaired fertility in males.

From: Medicines and Healthcare products Regulatory Agency (/government/organisations/medicines-and-healthcare-products-regulatory-agency)

Published 22 January 2024

Therapeutic area: **Neurology** (/drug-safety-update?therapeutic_area%5B%5D=neurology), **Obstetrics, gynaecology and fertility** (/drug-safety-update?therapeutic_area%5B%5D=obstetrics-gynaecology-fertility), **Psychiatry** (/drug-safety-update?therapeutic_area%5B%5D=psychiatry)

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These safety and educational materials support the new regulatory measures announced in the National Patient Safety Alert. (https://www.gov.uk/drug-device-alerts/national-patient-safety-alert-valproate-organisations-to-prepare-for-new-regulatory-measures-for-oversight-of-prescribing-to-new-patients-and-existing-female-patients-natpsa-slash-2023-slash-013-slash-mhra)

Healthcare professionals should review the new measures and materials and integrate them into their clinical practice when referring patients and when prescribing or dispensing valproate.

We are also reviewing data highlighted in Drug Safety Update August 2023 (https://www.gov.uk/drug-safety-update/valproate-re-analysis-of-study-on-risks-in-children-of-men-taking-valproate#:~:text=Valproate%20administration%20may%20also%20impair,of%20male%20infertility%20was%20unknown.), which may suggest an increased risk of

neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception. As a precaution we advise male patients who are planning a family within the next year, to discuss treatment options with a healthcare professional.

Advice for healthcare professionals:

- valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. For the majority of patients, other effective treatment options are available
- at their next annual specialist review, women of childbearing potential and girls receiving valproate should be reviewed using the revised valproate Annual Risk Acknowledgement Form. A second specialist signature will be needed if the patient is to continue on valproate, however subsequent annual reviews will only require one specialist
- general practice and pharmacy teams should continue to prescribe and dispense valproate and if required offer patients a referral to a specialist to discuss their treatment options. Valproate should be dispensed (https://www.gov.uk/government/publications/full-pack-dispensing-of-valproate-containing-medicines/full-pack-dispensing-of-valproate-containing-medicines) in the manufacturer's original full pack
- report suspected adverse drug reactions associated with valproate on a Yellow Card (http://www.mhra.gov.uk/yellowcard)

Advice for healthcare professionals to provide to patients:

- do not stop taking valproate without advice from a specialist. This is because epilepsy or bipolar disorder may worsen without treatment
- if you are on valproate, please attend any offered appointments to discuss your treatment plan and talk to a healthcare professional if you are concerned
- consult the Patient Information Leaflet (https://products.mhra.gov.uk/search/?search=valproate&page=1) and new Patient Guide (https://mhra-gov.filecamp.com/s/i/Zw7qR7wEy1YKeIEf) for information about the risks of valproate – see also the MHRA information page (https://www.gov.uk/government/collections/valproate-safety-measures) for resources
- as a precaution, male patients who are planning a family within the next year should speak to a healthcare professional about their treatment options

Valproate treatment and new safety measures

Exposure to valproate in pregnancy is associated with physical birth defects in 11% of babies and neurodevelopmental disorders in up to 30-40% of children, which may lead to permanent disability. Since 2018, valproate has been contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme (PPP) are followed.

In 2022, the Commission on Human Medicines (https://www.gov.uk/government/organisations/commission-on-human-medicines) (CHM) reviewed the latest data on the safety of valproate. The CHM heard from patients and other representatives about how valproate was being used and how the risks were currently managed. The CHM noted that data from the Medicine and Pregnancy Registry (https://digital.nhs.uk/data-and-information/publications/statistical/mi-medicines-and-pregnancy-registry) showed that pregnancies in England continue to be exposed to valproate.

The CHM also considered other known risks of valproate, including the risk of impaired male fertility. The CHM considered pre-clinical data on possible transgenerational risks with prenatal exposure, as well as data from studies in juvenile and adult animals suggesting adverse effects on the testes. There are currently limited data available on many of these risks in humans and further studies are planned. However, the CHM noted many patients receiving valproate have other therapeutic options with fewer potential reproductive harms.

On 28 November 2023, MHRA issued a National Patient Safety Alert (https://www.gov.uk/drug-device-alerts/national-patient-safety-alert-valproate-organisations-to-prepare-for-new-regulatory-measures-for-oversight-of-prescribing-to-new-patients-and-existing-female-patients-natpsa-slash-2023-slash-013-slash-mhra) to instruct Integrated Care Boards (in England), Health Boards (in Scotland), Health Boards (in Wales), and Health and Social Care Trusts (in Northern Ireland) to prepare for the new risk minimisation measures by 31 January 2024. The new safety and educational materials support these measures.

Due to the known significant risk of serious harm to a baby after exposure to valproate in pregnancy, these measures aim to ensure valproate is only used if other treatments are ineffective or not tolerated, and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme (PPP).

The CHM will consider further recent registry data (https://www.gov.uk/drug-safety-update/valproate-re-analysis-of-study-on-risks-in-children-of-men-taking-valproate) which may suggest an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception. In the study, around 5 children in 100 born to fathers treated with valproate around conception were diagnosed with a neurodevelopmental disorder. This is compared to 3 in 100 children whose fathers were taking lamotrigine or levetiracetam around conception (two other anti-seizure medicines). As a precaution male

patients on valproate who are planning a family within the next year should speak to a healthcare professional about their treatment options.

See the MHRA Public Assessment Report (https://www.gov.uk/government/publications/valproate-review-of-safety-data-and-expert-advice-on-management-of-risks) and MHRA website (https://www.gov.uk/government/collections/valproate-safety-measures), which will be added to in the coming weeks and months. The MHRA review of antiepileptic drugs in pregnancy (https://www.gov.uk/drug-safety-update/antiepileptic-drugs-in-pregnancy-updated-advice-following-comprehensive-safety-review) should also be consulted.

New Regulatory Safety and Educational Materials

To support the implementation of the new measures for valproate, the following safety and educational materials are being made available:

- Updated Healthcare Professional Guide (https://mhra-gov.filecamp.com/s/i/eGygqKVE00FH393c): Provides updated information for healthcare professionals on the risks of valproate in pregnancy and the risks for male patients, the new conditions for valproate prescribing and key points for patient discussions.
- Updated Patient guide (https://mhra-gov.filecamp.com/s/i/Zw7qR7wEy1YKeIEf): Provides those taking valproate (or their parent, caregiver, or responsible person) with updated information on the risks of valproate in pregnancy and the risks to male patients and what they need to do.
- Updated Annual Risk Acknowledgement Form (https://mhra-gov.filecamp.com/s/i/6iqrRqc0zoFgeEo7): For female patients starting valproate and at annual review. Used to support and record the discussion between the patient and specialist prescriber on the risks associated with valproate in pregnancy and to record the decision of the countersigning

specialist. At subsequent annual reviews only one specialist is required.

- New Risk Acknowledgement Form for male patients starting valproate (https://mhra-gov.filecamp.com/s/i/bEnPD49yZtHsXp3M): Used to support and record the discussion between the patient and specialist prescriber of the risks associated with valproate in males when starting treatment with valproate and to record the decision of the countersigning specialist. This is only to be completed at initiation of valproate.
- Patient card (https://mhra-gov.filecamp.com/s/i/yGUUvmiJbQFAj3Mc): Provides key information for female patients receiving valproate on contraception and pregnancy prevention.
- Pharmacy poster (https://mhra-gov.filecamp.com/s/i/dr66W7LuRQ3pY7u5): Provides important actions for pharmacists dispensing valproate to female patients.
- Warning stickers (https://mhra-gov.filecamp.com/s/i/T2hnHhs7A8MyvFKQ): To be added to packaging of medicine in exceptional circumstances where the original pack cannot be dispensed.

The updated product information and safety and educational materials are available on the MHRA website (https://www.gov.uk/government/collections/valproate-safety-measures) and the electronic Medicines Compendium (https://www.medicines.org.uk/emc/search?q=valproate). Links to the patient guide and patient card are also available via a QR code provided in the Patient Information Leaflets for Epilim and Depakote. The Marketing Authorisation Holders are sending a letter to healthcare professionals to support these changes with the hard copies of the materials which will begin distribution next week. On receipt of the new materials, healthcare professionals should discard previous versions of the valproate materials.

Further materials to support discussions with patients

Patients on valproate must be fully informed of the potential risks and counselled on their treatment options at the time of initial prescribing and at all subsequent reviews.

We ask clinicians to use appropriate individualised language when discussing the implications of taking valproate with patients and their caregivers.

The safety and educational materials should be used alongside other resources to support patients making decisions about valproate and other treatments for epilepsy and bipolar disorder. These include patient support tools, such as those published by the NHS (https://www.england.nhs.uk/publication/decision-support-tool-is-valproate-the-right-epilepsy-treatment-for-me/) and guidelines produced by the Association of British Neurologists. (https://cdn.ymaws.com/www.theabn.org/resource/resmgr/guidelines/abn_guidelines_for_valproate.pdf)

Report suspected reactions on a Yellow Card

Valproate is a black triangle medicine, and all suspected adverse reactions should be reported via the Yellow Card scheme. Reports can be made of suspected reactions experienced at any time, including historic adverse experiences with medicines.

Please include in the report as much detail as possible, particularly if a side effect continued or started after treatment was stopped. Information about medical history, any concomitant medication, onset timing, treatment dates, and product brand name should also be included.

Report to the Yellow Card scheme electronically using:

- the Yellow Card scheme website (https://yellowcard.mhra.gov.uk/)
- the Yellow Card app; download from the Apple App Store (https://itunes.apple.com/us/app/apple-store/id990237487?pt=117756671&ct=EYC&mt=8) or Google Play Store

(https://play.google.com/store/apps/details?id=uk.org.mhra.yellowcard&referrer=utm_source%3DEYC%26utm_medium%3Dcpc%26anid%3Dadmob)

- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

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