Medicines & Healthcare products Regulatory Agency

Valproate – managing reproductive risks in male patients under the age of 55 years

Public Assessment Report

Medicines and Healthcare products Regulatory Agency

February 2025

Contents

1. Plain Language Summary

Key messages: Valproate (as sodium valproate, valproate semisodium, or valproic acid; brand names Epilim, Depakote, Convulex, Episenta, Epival, Syonell, Belvo and Dyzantil) is approved in the UK to treat epilepsy and bipolar disorder. It is also sometimes used outside of the licence ('off label') to treat other conditions such as migraine.

No new patients under the age of 55 years should be started on valproate unless two specialists independently consider and document that other treatments do not work (i.e. are ineffective) or are not tolerated.

As a precautionary measure, it is recommended that male patients and their female partner should use effective contraception during valproate use and for at least 3 months after stopping valproate.

At their next annual specialist review, women and girls of childbearing potential receiving valproate should have their treatment reviewed using the revised Annual Risk Acknowledgement Form. At this review, if the patient has never been reviewed by two specialists either at initiation or annual review, a second specialist signature will be needed if the patient is to continue on valproate. Women do not need to be recalled for an additional review. Once a patient has received a treatment review by two specialists, subsequent annual reviews only require **one** specialist.

Patients on valproate should attend any offered appointments to discuss their treatment plan and talk to a healthcare professional if they are concerned.

No-one should stop taking valproate without advice from a specialist. This is because epilepsy or bipolar disorder may worsen without treatment.

Introduction to this report

The Medicines and Healthcare products Regulatory Agency (MHRA) regulates medicines, medical devices and blood components for transfusion in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. The Commission on Human Medicines (CHM) advises government ministers on the safety, efficacy and quality of medicines. This report provides an update on the advice of the CHM and the Valproate Implementation Expert Working Group (VIEWG) for male patients under 55 years of age currently taking valproate.

More information about the safety concerns for this medicine

Valproate can cause serious harm to an unborn baby if it is taken during pregnancy. Due to these risks, it has been advised for some time that valproate should only be used in female children or in any woman able to have children (women of childbearing potential) if other treatments do not work (ineffective) or are not tolerated. If valproate is used in women of childbearing potential, then the conditions of the Pregnancy Prevention Programme need to be followed. In 2022, in light of concerns that the regulatory requirements for safe use of valproate were not being consistently followed, particularly that pregnancies continued to be exposed to valproate, and emerging data on the risk of harms in male patients, the MHRA conducted a review of the available data and asked for advice from the independent CHM, which also listened to the views of patients and healthcare professionals.

The CHM advised that no one under the age of 55 should be started on valproate unless two specialists independently consider and document that other treatments do not work or are not tolerated. The CHM also advised that for existing patients under the age of 55 years, two specialists should independently consider and document that other treatments do not work or are not tolerated or that the risks do not apply to that individual patient.

The MHRA communicated this information to the UK public and to healthcare professionals in December 2022. After their review, the CHM formed the Valproate Implementation Expert Working Group (VIEWG) to advise on the safe introduction of the new measures into clinical practice.

The measures were applied first to all new patients under 55 years old and women already under specialist review. For men currently taking valproate the requirement for the two-specialist review was to begin in a subsequent phase of implementation, taking into account advice from healthcare professionals and patients developed in light of experience with the initial phase. On 28 November 2023 a National Patient Safety Alert was issued asking organisations to put a plan in place to implement the first phase of the new regulatory measures for valproate. The MHRA published an article in Drug Safety Update on 22 January 2024 announcing the availability of new safety and educational materials to support the new regulatory measures.

Reasons for the latest review and information considered

On 5 September 2024, based on a new study which suggested a possible risk of neurodevelopmental disorders to children born to fathers who take valproate, the MHRA issued new precautionary advice that male patients and their female partners should use effective contraception. At their meeting in September 2024, the CHM was asked to consider the new precautionary advice issued on 5 September and reconsider its previous advice that male patients under 55 years currently taking valproate should be reviewed and medication switched unless two independent specialists confirm this isn’t possible.

Advice from CHM

The CHM discussed the male reproductive risks with valproate in comparison to the robust evidence of significant harm from valproate use during pregnancy. The CHM discussed that the recently introduced risk minimisation measures should support informed decision making and prioritise men planning a family in the near future for discussions about switching their medications.

The CHM advised that the review by two specialists of male patients under 55 years currently taking valproate, was not required at this time. Given the requirement for two specialist review for male patients under 55 years newly starting valproate and the risk minimisation measures in relation to paternal risks, two specialist review of male patients under 55 years currently taking valproate is unlikely to minimise risks further in this patient group and would be associated with a significant clinical burden. The CHM advised that this position should be kept under review and that advice be sought from the VIEWG on the clinical pathway for male patients currently taking valproate and on how the impact of the new measures introduced in September 2024 should be monitored.

The VIEWG subsequently advised that annual review by a specialist and completion of an Annual Risk Acknowledgment Form for male patients taking valproate was not required. The VIEWG advised that a personalised clinical care plan in primary care for each patient was preferred over a regulatory form to record annual discussions with males and that the patient guide could support these discussions. The VIEWG advised that an update to the electronic healthcare system codes could help to both identify patients and record discussions have taken place. The VIEWG commented that although valproate is not a favoured medication for managing bipolar disorder in psychiatry, documentation of repeated discussions on risk are especially important for patients who have a fluctuating capacity as part of their condition. The VIEWG discussed the monitoring of the new measures for valproate and advised that data is needed to monitor potential unintended consequences of the regulatory action for valproate.

Next Steps

The MHRA is working with the Marketing Authorisation Holders to finalise safety and educational materials for male patients on valproate. The MHRA is continuing to monitor the impact of the risk minimisation measures for valproate.

2. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the regulator of medicines, medical devices and blood components for transfusion in the UK. The MHRA is responsible for making sure these products meet acceptable standards for safety, quality and efficacy. The Commission on Human Medicines (CHM) advises the government about medicines safety. The CHM is independent – it is not part of the government or the pharmaceutical industry.

In our safety Public Assessment Reports, we discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines.

Public Assessment Reports relating to previous reviews of valproate[1] were published by the European Medicines Agency in October 2014 and February 2018, and by the MHRA in November 2023 and September 2024.

In 2022, the CHM advised on new measures to increase the oversight of valproate prescribing in patients under the age of 55 years, with a new requirement that no new patients under the age of 55 years should be started on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment. The CHM also advised that all patients under 55 years should be reviewed, and medication switched unless two independent specialists confirm that this isn't possible (details of this consideration and the CHM advice are presented in the public assessment report published in November 2023).

On the advice of the Valproate Implementation Expert Working Group (VIEWG), these measures were introduced in a phased manner, with the initial phase applying to all patients under 55 years newly starting valproate and the prevalent female population of childbearing potential as these patients could be reviewed by two specialists at their next annual review. The CHM advised that for men currently taking valproate the requirement for the two specialist review should begin in a subsequent phase, taking into account advice from healthcare professionals and patients developed in light of experience of the initial phase.

In February 2024, the CHM and its Pharmacovigilance Expert Advisory Group considered the results of a Post Authorisation Safety Study on the paternal transmission of risk following use of valproate and issued precautionary advice that male patients and their female partners should use effective contraception while taking valproate and for 3 months after stopping valproate. This advice was communicated on 5 September 2024. In the context of these new risk minimisation measures introduced for all male patients taking valproate, the

[1] Valproate is used throughout to refer to sodium valproate, valproate semisodium, or valproic acid; brand names Epilim, Depakote, Convulex, Episenta, Epival, Syonell, Belvo and Dyzantil.

CHM was asked whether it wished to revisit any aspects of its advice of 2022 that male patients under 55 years currently taking valproate, should be reviewed, and medication switched unless two independent specialists confirm this isn't possible.

This report presents the current risk minimisation measures in place for men under 55 years taking valproate and the advice of the CHM on whether further regulatory action is appropriate. Changes have been made to the ordering and wording used in the original assessment report to aid readability and presentation.

A glossary is provided for an explanation of the terms used in this report.

The information and data contained in this report reflect evidence that was available at the time of the review in September 2024. The MHRA and CHM will continue to monitor the safety of valproate closely, however the information in this report will not be actively updated with new data or studies.

1. Background

In May 2022, the MHRA sought advice from the CHM following the release of data showing continued prescribing of valproate during pregnancy in England. Although use in female patients had declined 30% since the introduction of the Pregnancy Prevention Programme (PPP) in 2018, the data showed that the decline in prescribing had plateaued. It was noted that despite the introduction of the PPP there were still prescriptions of valproate being issued in the same month that a pregnancy was recorded. In addition, it was noted there was prescribing of valproate outside of the terms of its licence for prevention of migraine and in mental health conditions other than bipolar disorder.

The CHM considered the presented evidence of continued exposure of pregnancies to valproate in England and views of patients and their representatives at meetings in May and June 2022 on the adequacy of existing risk minimisation measures, in the context of additional safety signals under evaluation. These safety signals included:

- review of the published mechanistic evidence for the mode of action of valproate including reported epigenetic effects and histone deacetylase inhibitory properties

- updates on the risk of valproate-associated testicular toxicity in juvenile and adult animals and the uncertain clinical relevance to the male paediatric population

- consideration of the known risks of infertility in adult male patients

- pre-clinical data showing inter-generational and transgenerational effects of valproate as well as published data from a French charity survey reporting intergenerational effects of valproate in humans

- the potential for harm to children born to fathers taking valproate

On the basis of the data presented, in 2022 the CHM advised that there should be greater scrutiny of the way valproate is prescribed and that further risk minimisation measures were required – in particular that two specialists should independently consider and document that there is no other effective or tolerated treatment for patients under 55 years.

The CHM was conscious of the clinical implications of the new measures and asked that a Valproate Implementation Expert Working Group (VIEWG) be convened to advise on safe and effective introduction of the new measures. MHRA communicated the proposed changes in an article in Drug Safety Update in December 2022.

The VIEWG included representatives from professional bodies and healthcare system bodies including NHS England, the Care Quality Commission, the General Medical Council, the General Pharmaceutical Council, NICE, and the Devolved Administrations representing Scotland, Wales, and Northern Ireland.

The terms of reference of the VIEWG are to inform the CHM on:

- pathways and strategies for implementing the recommendations of the Commission on Human Medicines on valproate,

- communication and educational materials to support and record informed prescribing decisions,

- plans for measurement of compliance with the new regulatory requirements,

- plans for determining the impact of the updated regulatory position and associated communications.

The VIEWG met 11 times between October 2022 and September 2023 and reported back to the CHM several times on clinical considerations to support safe implementation of the new measures.

A summary of the main advice of the VIEWG on the first two aspects of their terms of reference is as follows:

- Implementation of the new regulatory position should be phased.

- Stakeholders should be made aware of the totality of the evidence including latest clinical data and in light of this data, the views of stakeholders should be sought on implementation plans.

- The two-signature approach should be configured to minimise any prescribing delays.

- Multi-Disciplinary Teams could be used to support two specialist decision-making.

- Clinical guidance is needed to interpret the new regulatory position and should be updated. Balanced decision-making tools should be developed with stakeholders.

- Implementation should be adequately resourced, including a digital Annual Risk Acknowledgement Form.

- Valproate-exposed pregnancies should be evaluated in a multidisciplinary framework, with learnings fed back to improve care.

- Further consideration should be given to flexibility of the two-specialist system, especially to address stakeholder concerns about impacts on autonomy.

- Systems should be in place as soon as possible to measure the outcome of the review

The CHM considered the advice of the VIEWG and feedback from other stakeholders on a number of occasions and in June 2023, on the basis of the totality of the evidence for harm and the availability of other treatment options for many patients where the benefit-risk would be more favourable, the CHM confirmed their previous advice that no new patients under the age of 55 years should be started on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment. The CHM advised that:

- the initial phase of implementation of the new regulatory position will apply to all patients under 55 years newly starting valproate and the prevalent female population (girls and women of childbearing potential).

- for girls and women already taking valproate the two-specialist system should be implemented at their next review.

- for men currently taking valproate the requirement for the two-specialist review will begin in a subsequent phase of implementation, which will take into account advice from healthcare professionals and patients developed in light of experience with the initial phase.

The evidence previously considered by the CHM, the advice of the VIEWG and the recommendations of the CHM are provided in the Public Assessment Report published in November 2023. On 28 November 2023 a National Patient Safety Alert was issued asking organisations to put a plan in place to implement the first phase of the new regulatory measures for valproate. MHRA published an article in Drug Safety Update on 22 January 2024 announcing the availability of new safety and educational materials to support the new regulatory measures.

2. Risk minimisation measures currently in place for male patients

In February 2024, the CHM and the Pharmacovigilance Expert Advisory Group considered the results of a Post Authorisation Safety Study which indicated a possible association between valproate use by men in the 3 months prior to conception and an increased risk of neurodevelopmental disorders in their children. The level of potential risk found in the study is substantially lower than the risk of neurodevelopmental disorders in children exposed to valproate in utero. The data considered by the CHM and the advice issued is available in the subsequent Public Assessment Report. On 5 September 2024, the MHRA published an article in Drug Safety Update with the precautionary advice that men and their partners should use effective contraception. The SmPC and PIL were updated and made available online. The MHRA is currently working with Marketing Authorisation Holders to update the following safety and educational materials with this new risk:

- Patient card
- Patient guide – there will be separate guides for male and female patients
- Risk acknowledgment form for male patients starting valproate
- Healthcare professional guide

Once finalised these materials will be available online on the electronic medicines compendium and the MHRA website and will be sent in hard copy to healthcare professionals.

3. Usage data

Data from the NHS Business Services Authority suggest that between March 2024 and February 2024 there were approximately 60,000 male patients aged 13 to 54 being prescribed valproate in England with an additional 5,000 aged 12 and younger.

There is some early indication of an impact from the implementation of the two specialist system for new female patients. Data from the NHS Business Services Authority suggests that between December 2022 and June 2024 the number of women of aged 13 to 54 starting valproate in England dropped by approximately 30%.

4. NICE

In January 2025, NICE published its updated Epilepsies in children, young people and adults guideline (NG217) which takes into account the new regulatory position for valproate in males.

5. Current regulatory position and advice sought

The regulatory position for male patients on valproate had changed since the CHM previously provided advice in June 2022. The first phase of implementation which began in January 2024, introduced the two specialist system for all patients under 55 newly initiating valproate and for women and girls of childbearing potential continuing valproate and a risk acknowledgment form for male patients aged under 55 years to be used at initiation of treatment with valproate.

The changes implemented in the SmPC and PIL as a result of the paternal PASS include for the first time, a recommendation for regular review of male patients taking valproate.

SmPC

'Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.'

PIL

‘You should get regular appointments with your GP. During this visit your GP will discuss with you the precautions associated with valproate use. They will refer you to a specialist to discuss the possibility of other treatments that can be used to treat your disease, depending on your individual situation.’

The article in Drug Safety Update on 5 September 2024 gave the following advice for healthcare professionals:

- *‘inform male patients (of any age) who may father children of the possible risk at initiation of valproate or at their next regular treatment review – this counselling should be given irrespective of the indication for valproate and also after intravenous use of valproate*

- *as a precaution, recommend that male patients use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate, to allow for one completed sperm cycle not exposed to valproate*

- *at the next regular treatment review, discuss with men on oral valproate treatment whether they are planning a family in the next year and if they are, refer to a specialist to discuss alternative treatment options*

- *if a female patient reports they are pregnant or planning a pregnancy with a man on valproate (including those undergoing IVF), refer for prenatal counselling*

- *advise men not to donate sperm during valproate treatment and for 3 months after stopping valproate‘*

Updated safety and educational materials will include an updated risk acknowledgment form to be used at initiation of valproate, an updated patient card which will be provided with every pack and include information about the paternal risk alongside information about the Pregnancy Prevention Programme for women and a separate patient guide for male patients which will bring all the reproductive risks applicable to male patients together in one place. We have sought the views of the Valproate Stakeholder Network on the new draft materials.

We will be monitoring the impact of the additional risk minimisation measures for male patients using a number of different data sources including prescribing data and we will be seeking feedback from the Valproate Stakeholder Network on the practical implications of the new measures. It will take some time before we see the full impact of these new measures.

At their meeting of September 2024, the CHM was reminded of its previous advice from 2022, of:

- no new patients under the age of 55 years should be started on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment.

- all patients under 55 years should be reviewed, and medication switched unless two independent specialists confirm that this isn't possible.

These measures had been introduced in a phased manner with the initial phase (in January 2024) applying to all patients under 55 years newly starting valproate and the prevalent female population of childbearing potential. For men currently taking valproate, the CHM had previously recommended that the requirement for two specialists to review patients should begin in a subsequent phase, taking into account feedback on lived experience and any available data relating to the initial phase.

The CHM was asked to consider whether the advice of June 2022 in relation to the prevalent male population was warranted at this time, in the context of the additional risk minimisation measures which had been introduced in September 2024 in response to the Post Authorisation Safety Study on the paternal transmission of risk with valproate.

6. CHM advice

The CHM noted that there is now a recommendation in place that male patients and their female partners should use effective contraception while taking valproate and for 3 months after stopping. Men will be made aware of the need to use contraception by information on the patient card provided when valproate is dispensed and that if they are planning a family, to discuss with their GP the need to be referred to a specialist to discuss other treatment options. The CHM noted that there was also work ongoing to update the risk acknowledgement form for male patients starting valproate and to create a separate patient guide for male patients on the reproductive risks.

The CHM discussed the nature and magnitude of the male reproductive risks with valproate in comparison to the robust evidence of significant harm from valproate use during pregnancy. The CHM discussed that the recently introduced risk minimisation measures should support informed decision making and prioritise men planning a family in the near future for discussions about switching their medications.

The CHM advised that in the context of the requirement for two specialist sign off for male patients under 55 years newly starting valproate and the risk minimisation measures announced for all male patients in relation to paternal risks, review of male patients under 55 years currently taking valproate by two specialists was not required at this time as it is unlikely to minimise risks further in this patient group and would be associated with a significant clinical burden. The CHM advised that this position should be kept under review.

The CHM asked that the VIEWG consider the clinical pathway for male patients currently taking valproate in primary care and whether the current guidance for regular review needs to include a method of documenting the discussion such as an annual risk acknowledgement form.

The CHM emphasised that it was important that MHRA continue to work with the healthcare system to support safe use of valproate.

The VIEWG subsequently advised that:

- annual review by a specialist and completion of an Annual Risk Acknowledgment Form for male patients treated with valproate was not required.

- a personalised clinical care plan in primary care for each patient was preferred over a regulatory form to record annual discussions with males and that the patient guide could support these discussions.

- an update to the electronic healthcare system codes could help to both identify patients and record discussions have taken place.

The VIEWG further commented that although valproate is not a favoured medication for managing bipolar disorder in psychiatry, documentation of repeated discussions on risk are especially important for patients who have a fluctuating capacity as part of their condition.

The VIEWG discussed the monitoring of the new measures for valproate and advised that data is needed to monitor potential unintended consequences of the regulatory action for valproate. In addition, the VIEWG suggested that there should be external communication from MHRA to inform the public that the MHRA is aware of the risk of potential unintended consequences and to convey how the MHRA plans to monitor these outcomes.

7. Next steps

The MHRA is currently working with Marketing Authorisation Holders to finalise safety and educational materials for male patients. The MHRA is continuing to monitor the impact of new risk minimisation measures for valproate.

8. Glossary of terms

Commission on Human Medicines
The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products.

Patient Information Leaflet
Medicine packs includes a Patient Information Leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics (SPCs) which are a description of a medicinal product's properties and the conditions attached to its use.

Summary of Product Characteristics (SmPC)
Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use, which is available at: https://www.gov.uk/guidance/find-product-information-about-medicines