

Memo - Precautionary Safety Advice for Men Prescribed Valproate

Issued in response to [September 2024 MHRA Drug Safety Update Valproate Use in Men](#) *This local guidance is applicable to anyone who can biologically father children, including men or trans-women who retain the capability to generate sperm.

Advise NOT to stop taking Valproate without the advice of a specialist as this will risk worsening the condition.

Valproate Potential risks in Males

Valproate may cause infertility in men, with some toxic effects observed on the testes in animal studies, though its significance is unclear for humans. A meta-analysis found a slightly higher risk of neurodevelopmental disorders in children born to males taking valproate (4.0-5.6%) compared to those on other epilepsy drugs (2.3-3.2%), with an adjusted hazard ratio of 1.50. However, this risk is much lower than the 30-40% risk observed in children born to mothers taking valproate during pregnancy. For detailed information, refer to the [Public Assessment Report on Valproate Safety Data](#).

Precautionary Advice from MHRA for Male Patients Prescribed Valproate

Males prescribed valproate (includes following intravenous administration) should be informed about potential risks and the need to use effective contraception.

Practical Tips: Contraception and Birth Control Advice

- Recommend male patient and his female sexual partner should both use effective birth control (condoms and another form of female contraception). The reason for using two forms of birth control is because condoms are not always effective at preventing pregnancy*.
(*Note: If the woman is already using *highly effective* contraception condoms may not be required)
- Birth control measure should be in place while on valproate and for at least 3 months after stopping valproate.
- Advise male patients NOT to donate sperm while prescribed valproate and for 3 months after stopping treatment.
- Those planning a family in the next year, including in those planning IVF, should be referred to a specialist to discuss their treatment options and prenatal counselling should be provided.
- Consultations about the risks and advice on condoms and effective contraception for female partners should be documented in clinical notes.

As reproductive potential in males continues beyond 55 years, ALL men who can biologically father children should also be counselled on the risk and precautions as appropriate.

The MHRA have produced the following tools to support conversations

- [Advice for male patients on valproate to use contraception](#)
- [Visual risk communication diagram to be used by a healthcare professional when counselling on the risks](#)

Safety Measures for Existing Male Patients on Valproate

There is no requirement for a RAF to be completed. The MHRA advice is that male patients **should be informed about the risk** and counselled on the use of effective contraception.

Practical Tips: Safety Measures for Existing Male patients

- All men and trans-women who can biologically father children currently taking valproate should be informed about the potential risks. There is a professional responsibility and failure to inform the patients of the risk may leave the prescriber open to a claim or complaint to the regulators. This risk should be communicated in a way that best suits the individual patient's needs.
- Practices can consider a simple signposting message advising that new potential risks have been observed, include a link to the MHRA patient information [Advice for male patients on valproate to use contraception](#) and a reminder not to stop taking valproate without discussing it with a healthcare professional. Offer an opportunity to discuss at the next routine medication review or sooner if they wish.
- Electronic messaging is commonplace (example being AccuRX message) and the practice may consider this appropriate for some or all of their patients. Practice should exercise caution and apply reasonable adjustment in communication method to tailor to the patient's individual's needs e.g. LD, language or communication barriers.
- No requirement to refer existing male patients to specialist, unless the patient has concern and wishes to discuss their treatment options. It is anticipated that discussions about treatment options in epilepsy or bipolar disorder is out-of-scope of practice for majority of primary care clinicians.

Safety Regulatory Measures for Valproate Male new starters

Aim to reduce prescribing of valproate only to male patients where no other therapeutic options are suitable, and ensure patients are informed and understand the risk and this is documented via a formal signed risk acknowledgement form.

Practical Tips: Safety Regulatory Measures for Male New Starter

- Since January 2024, Valproate should not be started in male patients aged under 55 years unless two specialists consider and document on the [Male Risk Acknowledgement Form](#) (ARAF) that there is no other effective or tolerated treatment or the risk of infertility or potential risk of testicular toxicity do not apply.
- The male patient RAF is only required to be completed once and does not need to be repeated annually.

A collection of information and patient guide resources can be found in [Valproate safety measures - GOV.UK \(www.gov.uk\)](#)

Flowchart summary advice for Safe Valproate Prescribing in Men*

Advise NOT to stop taking Valproate without the advice of a specialist as this will risk worsening the condition

New-Starter of Valproate in Male age under 55 Years Identified

- At the point of taking on continue prescribing responsibility, ascertain that a [Male Risk Acknowledgement Form](#) has been completed by the initiating specialist(s), shared and documented in your clinical system.

Is a completed Male RAF available?

Yes

No

Record the receipt of the RAF if completed
Risk Acknowledgement Form for Male Patients Starting Valproate completed (Ycj8h)

Contact initiating specialists to forward a completed Male RAF form in order for you to continue prescribing in accordance with MHRA guidelines.

The male patient RAF is only required to be completed once and does **NOT** need to be repeated annually.

Provide Contraception and Birth Control Advice

- Recommend male patient and his female sexual partner should both use effective birth control (condoms and another form of female contraception). The reason for using two forms of birth control is because condoms are not always effective at preventing pregnancy*.
- (*Note: If the woman is already using *highly effective* contraception condoms may not be required, FSRH advises highly effective contraception would include sterilization and LARCs: copper IUDs, levonorgestrel IUSs, and progesterone-only implants (all have typical use failure rate <1%). COCP and POPs have a typical use failure rate <9%, and progestogen-only injectables (DMPA) (although still a LARC) have typical use failure rate of <6%; therefore, they are not considered highly effective methods of contraception. [Medicines with teratogenic potential: what is effective contraception and how often is pregnancy testing needed? - GOV.UK \(www.gov.uk\)](#))
- Birth control measure should be in place while on valproate and for at least 3 months after stopping valproate.
- Advise male patients should not donate sperm while prescribed valproate and for 3 months after stopping treatment.
- Those planning a family in the next year, including those planning IVF, should be referred to a specialist to discuss their treatment options and prenatal counselling should be provided.
- Consultations about the risks and advice on condoms and effective contraception for female partners should be documented in clinical notes.

Identify existing male patient(s) on valproate containing product

Searches to identify male prescribed valproate containing products on repeat can be found here-[Reporting> Clinical Reporting> BSW General Practice > Medicine Optimisation Team > f Valproate> Review MHRA Precautionary Safety Advice: Male patient with valproate containing products on repeat](#)
Practices should consider that when searching their system for patients trans women may not appear in the search results

Ascertain biological capability to father children

All men and trans-women who can biologically father children currently taking valproate should be informed about the potential risks

Yes

No

Documented reason of biological capability father children or risk of infertility do not apply

- Offer an opportunity to discuss at the next routine medication review or sooner if they wish.
- Consider, sending a simple signposting message** advising that new potential risks have been observed and effective birth control. **Include a link to the MHRA patient information advice and a reminder not to stop taking valproate** without discussing it with a healthcare professional.
- MHRA information leaflet for Male** [Advice for male patients on valproate to use contraception](#)
- Exercise caution and apply reasonable adjustment to communication method to tailor to the individual patient's needs e.g. LD, language or communication barriers.
- Advice given on risks and advice on condoms and effective contraception for female partners should be documented in clinical notes.

No requirement to refer existing male patients to specialist, as a result of these paternal risks, unless

- patient has concern and wishes to discuss their treatment options. It is anticipated that discussions about treatment options in epilepsy or bipolar disorder is out-of-scope of practice for majority of primary care clinicians.
- patient who are planning a family within the next one to two years should speak to healthcare professional about their treatment.

Some Common Questions and Answers (Q&A):

Q: When will risk materials (e.g. Patient Guide) be updated?

A: There may be a delay between the publication of the MHRA Drug Safety Update and amendments by the manufactureres to the risk materials such as the Valproate Patient Guide. Once available updated risk materials will be available within the product summaries 'Risk Materials' section see <https://www.medicines.org.uk/emc> & [Valproate safety measures - GOV.UK \(www.gov.uk\)](https://www.gov.uk/government/news/valproate-safety-measures)

Q: Who in the practice can hold a consultation about the potential paternal risks?

A: Any registered healthcare professional, such as GPs, Pharmacists and Nurses who are competent and confident to complete the consultation.

Q: Do all men (and trans-women who can father children) need to have a Risk Acknowledgement Form (RAF) completed?

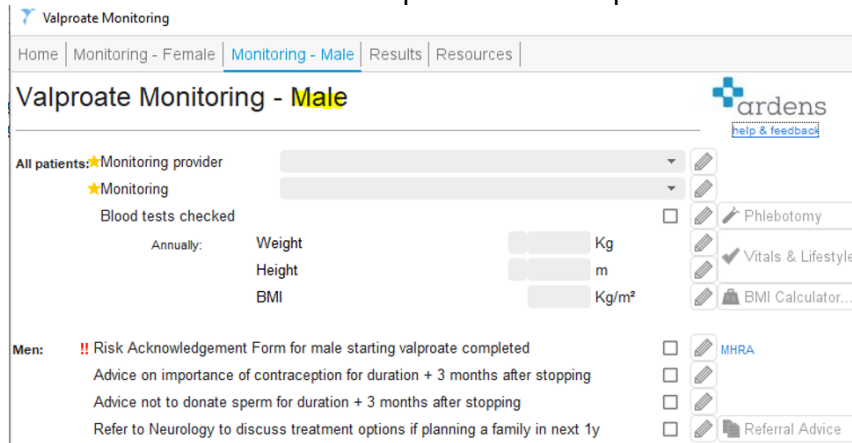
A: No. Only those who have been initiated on valproate after the 31st of Jan 2024 will have a RAF. This will be completed by the initiating specialist. Once only.

Q: How should the practice document and code that the patient has been informed about the paternal risks and advice for effective contraception?

A: Utilise Ardens's Valproate Monitoring Male Template – see pictures below

For new male patients the practice can record the receipt of the RAF using "Risk Acknowledgement Form for Male Patients Starting Valproate completed (Ycj8h)"

For new and existing valproate patients, document advice on importance of contraception and not to donate sperm. Consultations about the risks and advice on condoms and effective contraception for female partners should also be documented in clinical notes.



(Arden's Resources: Valproate Monitoring Template for Male)

Q: What should I do if a person expresses concern that their child or children might have been affected by paternal exposure to valproate.

A: Establish if the use of valproate was within 3 months of conception. Discuss the potential risks have been shown when sperm have been exposed to valproate (at any point in the cycle which produces sperm which is slightly less than 3 months) but the potential risks have not been studied when valproate was stopped more than 3 months before conception. Advise them of the relative risks and the uncertainty of the causal nature of valproate. We do not currently know if the Neurodevelopmental Disorder (NDD) caused by valproate taken by fathers can be distinguished from baseline incidence. Follow local protocols for referral to a specialist for neurodevelopmental disorders if the parents are concerned and the affected person has displayed signs of an NDD. The following charities may be able to give advice and support [Home – INFAC \(infactuk.com\)](https://infactuk.com) & [Organisation for Anti-Convulsant Syndrome | Valproate | Epilim \(oacscharity.org\)](https://oacscharity.org)

Further advice may be issued by Royal Collages as consensus emerges which may supersede this document.

Supporting Information

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

➤ Risk Acknowledgement Forms:

- **Male:** [Male Risk Acknowledgement Form](#), 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.

➤ MHRA have produced the following tools to support conversations

- [Advice for male patients on valproate to use contraception](#)
- [Visual risk communication diagram to be used by a healthcare professional when counselling on the risks](#)

➤ [Healthcare Professional Guide](#): 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.

➤ Patient guides for [female](#) and [male](#) patients: provide 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.

➤ [Electronic Medicines Compendium](#). 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.

➤ Patient Support Networks: [Bipolar UK](#) - 0333 323 3880, [Epilepsy Action](#) - 0808 800 5050, [Epilepsy Society](#) - 01494 601 400, [Mind](#) - 0300 123 3393. INFACT - [Home – INFACT \(infactuk.com\)](#) who provide information, advice and support to families. OACS - [Organisation for Anti-Convulsant Syndrome | Valproate | Epilim \(oacscharity.org\)](#) who provide support to all families touched by Fetal Anticonvulsant Syndrome. For patients who have questions or concerns about the risks associated with valproate, please speak to your doctor, pharmacist or other healthcare professional.

➤ Where relevant, ensure the patient is aware of the obligation to inform the DVLA about a medical condition or disability or regular medication that affects driving <https://www.gov.uk/driving-medical-conditions>

BSW Specialist Contacts

Do not routinely refer existing male patients to specialist, as a result of these paternal risks, unless

- patient has concern and wishes to discuss their treatment options. It is anticipated that discussions about treatment options in epilepsy or bipolar disorder is out-of-scope of practice for majority of primary care clinicians.
- patient who are planning a family within the next one to two years should speak to healthcare professional about their treatment.

BSW local Neurology teams can be contacted for advice on treatment options via Cinapsis – Advice and Guidance.