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Norfolk and Waveney Integrated Care System

Management of valproate in primary care:

guidance for prescribing in new patients and existing female patients of childbearing potential

Document Control Sheet

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Name of document:	**Prescribing of valproate in Primary care: guidance for the use in women and men under the age of 55 years**
Ref Number:	**N/A**
Version:	**V0.4**
Date of this version:	**April 2024**
Produced by:	NWICB Medicines Optimisation Team alongside the Medicines Safety Officer Valproate alert working group.
What is it for?	The guidance is to support GPs with prescribing valproate in accordance with the 2023 MHRA alert.
Evidence base:	• Medicines and Healthcare products Regulatory Agency. organisations to prepare for new regulatory measures for oversight of prescribing to new patients and existing female patients
Who is it aimed at and which settings?	The policy applies to all staff involved with the prescribing and ongoing monitoring of valproate across all settings of Norfolk and Waveney ICB
Impact Assessment:	Equality Impact Assessment - no adverse impact Data Protection Impact Assessment not required.
Other relevant approved documents:	• Specialist Pharmacy Service. Valproic acid and sodium valproate monitoring • SPC for sodium valproate, semi sodium valproate and valproic acid.
References:	• See end of document
Training and competencies	Staff involved with the prescribing and monitoring of valproate must be competent and aware of the 2023 MHRA alert.
Monitoring and Evaluation	This policy will be monitored and reviewed for effectiveness by the Medicines Optimisation Team
Consultation:	The three acute trusts, mental health services, 2 community services, primary care and sexual health clinic have all input into this document.
Reviewed by:	NWICB MSO valproate alert working group
Approved by:	TAG / MOPB
Date approved:	June 2024
Dissemination:	NWICB Intranet
Date disseminated:	August 2024
Review Date:	April 2025 (or sooner if regulatory changes)
Contact for Review:	nwicb.medsqueries@nhs.net

Contents

1.0 Introduction

Valproate is a medication used in the treatment of epilepsy and bipolar. It is sometimes used to treat other conditions, including migraines, although these indications are unlicensed.

In the UK valproate comes in three chemical forms: sodium valproate, valproate semi-sodium and valproic acid[1]. Commonly prescribed brands of valproate include Epilim®, Depakote®, Convulex®, Episenta®, Epival®, Kentlim®, Orlept®, Syonell®, Valpal®, Belvo®, Dyzantil®.

Over the past few years there has been a growing amount of evidence that the use of valproate in women during pregnancy can lead to serious adverse effects in the unborn baby. For women who take valproate during pregnancy around 11% of babies will have a birth defect compared to 2-3% of the general population[2]. Birth defects can be severe and include spina bifida, problems with hearing and vision and malformation of limbs, organs and skull. It is also known that valproate taking during pregnancy also increases the risk of neurodevelopmental disorders in between 30-40% of children[2].

Due to the known risks of valproate exposure to unborn babies during pregnancy, the Medicines and Healthcare products Regulatory Agency (MHRA) issued an alert in 2018[3] stating that girls or women of childbearing potential should not be prescribed valproate unless the terms of the Pregnancy Prevention Programme (PPP), known as PREVENT, are met. Further regulatory changes have been introduced by the MHRA via a National Patient Safety alert issued in November 2023[2] and came into effect in January 2024. These changes relate only to oral valproate preparations. They bring greater scrutiny to the prescribing of valproate in girls and women of childbearing potential, including the need to have two separate specialists sign the required Annual Risk Assessment Form (RAF).

The regulatory changes within the most recent alert extends to males under the age of 55 years old being initiated on valproate. This is due to emerging evidence of reduced fertility in men taking valproate and possible neurodevelopment disorders in children born to men taking valproate. Further regulatory changes to males already taking valproate are expected towards the end of 2024.

2.0 Primary Care Responsibilities

All healthcare professionals involved in the prescribing or monitoring of valproate must be familiar with the 2023 MHRA alert for valproate and have read the 'Guide for Healthcare Professionals'[4]

It is important that GP practices have a clear oversight of **all** female patients under the age of 55 years prescribed valproate, regardless of childbearing potential. Searches to identify these patients have been provided by the Medicines Optimisation team at NWICB for both SystmOne and EMIS Web. If further support is needed with the searches, please contact the team via nwib.medsqueries@nhs.net. It is strongly suggested that GP surgeries run a regular audit to ensure females under the age of 55 years with childbearing potential meet the conditions of the PREVENT pregnancy programme. CQC will also seek assurances that the recent MHRA alert relating to valproate has been handled appropriately as part of their inspection criteria.

2.1 Initial Assessment and Referral by the GP for patients prescribed valproate

Prescribing of valproate in primary care in females under the age of 55 years should only occur under guidance from a relevant specialist. This is reflected in the recent changes to the TAG status of valproate within Norfolk and Waveney ICB (NWICB). It anticipated that towards the end of 2024, this will extend to males under the age of 55 years.

2.2 Management of girls and women under 55 years of childbearing potential

GP surgeries should ensure a regular search is run within their patient management system to identify girls and women under the age of 55 years prescribed valproate. The purpose of the search is to ensure valproate prescribing meets the terms of PREVENT. The following checks should be made against the flowchart in appendix 1.

Due to the regulatory changes in the 2023 MHRA alert[2], women under the age of 55 years prescribed valproate who are not currently under the care of a specialist will need referral. This is because the responsibility of ensuring an annual review and ARAF is completed remains with secondary care. Referrals should be completed using the referral form in appendix 2.

Ensure all women and girls have been provided the updated patient information guide[1]. Hard copies of this guide can be ordered via Sanofi Medicines Information department by email UK-Medicalinformation@sanofi.com or phone 0800 035 2525.

2.21 Highly effective contraception

Where it has been identified that the patient is not using highly effective contraception and has capacity, a discussion with the patient must be undertaken regarding the importance of using **highly effective** contraception or abstaining from sexual intercourse.

Highly effective contraception has a typical-use failure rate of less than 1% and include long-acting reversible contraceptive (LARC) methods, such as intrauterine devices and implants, and progesterone-only injections provided they have been recorded as administered on schedule by a healthcare professional. The use of combined hormonal contraceptive (pills, patches, or vaginal rings), and progestogen-only pills have a typical-use failure rate of 9% and are therefore not deemed as effective contraception[5].

Where the patient agrees to contraception an urgent appointment should be made with either the practice nurse (if the surgery offers LARC services) or referral should be made to the sexual health clinic via the referral form (appendix 3).

If the patient refuses the use of highly effective contraception following discussion, management of the patient may need to remain with the specialist as the terms of PREVENT have not been met. This decision should be taken on a case-by-case basis following discussion with the patient and specialist and taking into consideration the patient's individual circumstances. It is recognised that female patients do have the right to refuse contraception and this should be based on an informed decision following a discussion of the risks versus benefits. Where these situations arise, clear document of this decision must be made in the patient's clinical record.

In exceptional circumstances, contraception may not be required including where the chance of pregnancy is deemed low, for example female sterilisation, hysterectomy or severe learning difficulties where sexual intercourse is unlikely. Where highly effective contraception is not considered necessary, the reasons for this must be clearly documented on the ARAF by the prescribing specialist and then appropriately read coded within the patient notes.

2.22 Pregnancy in females prescribed valproate

All female patients prescribed valproate who are pregnant, or express plans to start a family within the next 12 months must be referred to their specialist without delay for further advice (within days).

Patients planning a pregnancy must be encouraged to continue using highly effective contraception until reviewed by the specialist. It remains the responsibility of the specialist to review whether treatment with valproate remains in the patient's best interest in pregnancy and the risks versus benefits must be discussed with the patient.

Where there is a risk of pregnancy, a serum pregnancy test must be offered at least 14 days after the last possible date on which the patient had or could have had unprotected sexual intercourse or sexual intercourse without highly effective contraception in place.

The use of valproate in epilepsy is unlicensed in pregnancy and should only be prescribed where there is no other effective or tolerated treatment[6]. Valproate is contra-indicated in pregnancy for the treatment of bipolar and therefore specialists should review the patient as soon as possible for a tapering dose reduction[6].

2.3 Management of girls and women under 55 years with no childbearing potential and those exempt from PREVENT

The recent regulatory changes stipulate that **all** females prescribed valproate under the age of 55 years must have an updated ARAF form completed at their next annual review. This includes patients currently exempt from the PREVENT programme. It is acknowledged that some of these patients will no longer be under specialist care and therefore a referral to secondary care will be required using the referral form in appendix 2.

For some patients, this may be a potentially distressing conversation and therefore please ensure that the referral form details as much information as available on the current exemption criteria.

Where deemed clinically appropriate by two specialists reviewing the valproate prescribing, the patient can be exempted from the PREVENT programme and therefore a one-off ARAF form can be completed.

2.4 Annual Risk Assessment Forms

Completed forms must be uploaded onto the patient management system once received. Forms should be checked to ensure the patient has also signed in the designated box before uploading.

If the patient does not have a completed form this should be followed up by either contacting the patient (in the event they have not signed the form) or referral to the specialist without delay where an ARAF has not been sent.

The following codes should be used:

- Valid Risk Assessment completed: Valproate Annual Risk Acknowledgement "Form completed" SCTID: 1366401000000107 (SystmOne *Y362e*)
- Referral made for completion of risk assessment: "Referral for completion of" Valproate Annual Risk Acknowledgement Form SCTID: 1366381000000107 (SystmOne Y38a6)

NWICB strongly suggest the Ardens template for 'Valproate Monitoring' is used for this purpose (appendix 4).

It is also suggested that where valproate is listed as a repeat prescription item, the date of the RAF is recorded in the script notes. The expiry date for any repeat templates of valproate should be set to the month the ARAF expires to prevent prescriptions being issued beyond this date.

Where a one-off RAF is completed this should be documented in the patient notes and recorded in the script notes.

2.5 Prescribing of valproate

Prescribing in primary care should be in accordance with local formulary decisions.

The prescribing clinician must be satisfied that the conditions of PREVENT are met for all prescription requests for females of childbearing potential. If there is any doubt it is the responsibility of the clinician signing the prescription to review and, where necessary discuss with the patient.

In October 2023 the MHRA[8] issued legislative changes on the requirement dispensing of valproate in the manufacture's original **full pack**. This is to ensure that women always receive information about the harms of valproate during pregnancy. When prescribing valproate always ensure the nearest full pack is issued. In exceptional circumstances, for example where a monitored dosage system is in place, smaller quantities may be dispensed provided the dispensing pharmacy has completed a risk assessment.

2.6 Coding and Recalls

All surgeries must have a robust process in place for patient recall for annual reviews. To aid with effective recalls, patients must be appropriately read coded so they can be quickly identified. This includes read codes to indicate that a completed and valid ARAF is in place. Using the Ardens template for valproate monitoring will help to ensure the most appropriate read codes are used.

2.7 Medication reviews

All patients prescribed valproate must have a medication review undertaken by an appropriate clinician at least annually. This must be recorded in detail within the patient's notes, ideally using the Ardens 'Valproate monitoring' template. The medication review must be undertaken with reference to local formulary decision and must cover the following points as a minimum:

Monitoring requirements

- At least annual monitoring for the following should be undertaken: FBC, LFTs including prothrombin time, weight and BMI[9]. Any abnormal results should be communicated to the specialist.
- Please note, where the review is part of a wider annual review, for example a Severe Mental Illness (SMI) annual review, additional monitoring may be required.

Annual Risk Assessment Form

- Check to ensure an ARAF completed by the patient's specialist is present and has been read coded within the patient notes. Where this is not completed or has expired, a referral should be made to specialist care. The patient must be made aware of the date the next ARAF is due.
- Where there is a permanent absence of the risk of pregnancy (i.e. post-menopausal, hysterectomy etc) this has been clearly stated on the ARAF and is clearly documented and read coded in the patient notes.

Pregnancy Prevention Programme

- Ensure where there is a risk of pregnancy the patient has been enrolled onto the PPP.
- The use of highly effective contraception must be discussed and the patient's understanding of the importance of its use whilst prescribed valproate checked.

- Where highly effective contraception is not in place and the patient is willing to commence, an urgent referral must be made for highly effective contraception to be initiated (i.e. practice nurse, sexual health clinic). The importance of abstaining from sexual intercourse or the interim use of two effective contraception must be discussed and documented.

- Where highly effective contraception is not is use and the patient does not consent to its use, advice from the specialist must be sought following a discussion with the patient, including the risks of pregnancy during valproate.
- The patient must be reminded that where pregnancy is suspected or the patient is planning a pregnancy, to report this urgently. The patient must be reminded to continue to take their valproate as prescribed.
- The following read codes are recommended:

	SystmOne code	SNOMED Concept ID
Pregnancy Prevention Programme started *To be used when an ARAF is received from secondary care and ongoing annual reviews are required*	Y2f16	1129771000000103
Pregnancy Prevention Programme declined *To be used the patient has been referred to secondary care, was given an appointment for ARAF completion but did not attend*	Y2f17	1129801000000100
Pregnancy Prevention Programme not needed *To be used when an ARAF is received from secondary care and ongoing annual reviews are not needed, for example, a patient who is of childbearing age but has had a hysterectomy*	Y2f18	1129791000000104
Pregnancy Prevention Programme discontinued	Y2f19	1129841000000102
Did not attend Pregnancy Prevention Programme	Y2f1a	1129831000000106
Pregnancy Prevention Programme declined by parent	Y2f1b	1129821000000109
Pregnancy Prevention Programme declined caregiver	Y2f1c	1129811000000103
Valproate Annual Risk Acknowledgement Form completed *To be used when Valproate ARAF received from secondary care*	Y362e	1366401000000107
Referral for completion of Valproate Annual Risk Acknowledgement Form *To be used when a referral has been made from primary care to secondary care*	Y38a6	1366381000000107

Pregnancy Testing

- Discuss the need for pregnancy testing if appropriate. For example, when changing contraception methods, where there is potential to lack of adherence to contraception or where effective contraception is in place which is user-dependant.
- Where the patient has had, or could have had, unprotected sexual intercourse of sexual intercourse without the use of highly effective contraception, at least 14 days preceding the review, a serum pregnancy test must be offered.
- Signpost to appropriate services that can offer free pregnancy testing.

Adverse Effects

- Discuss possible side effects and signs and symptoms of these, including blood dyscrasias, liver dysfunction, pancreatitis, and suicidal ideation.
- Valproate is a black triangle medication; any suspected adverse reactions must be reported to the MHRA via the Yellow Card Scheme.

2.71 Structured Medication reviews

The Network Contract Directed Enhanced Service[10] suggests undertaking a Structure Medication Review (SMR) for medication with the potential to cause harm. Valproate prescribing in women of childbearing potential would be included as a medication with potential to cause harm and therefore it is good practice to complete a SMR at least at least annually. A SMR differs from an annual medication and therefore should be read coded as such.

2.8 Management of Males prescribed valproate

2.81 Males under 55 years newly initiated on valproate

The most recent changes to the regulations stipulate males should not be initiated on a valproate containing medicine unless two specialists consider and document there is no other effective or tolerated treatment or the risk of infertility or potential risk of testicular toxicity do not apply. The exception to this is where the risks do not apply, for example the patient is permanently infertile, in which case the countersigning specialists is not required[7]. The specialist must document any exemption on the Risk Assessment Form (RAF) and this reason should be read coded appropriately within the GP system. In male patients under the age of 55 years, the RAF form only needs to be completed at the point of initiation of valproate.

The GP surgery is responsible for ensuring that any male patients under the age of 55 years has received a completed RAF prior to prescribing. The RAF must be uploaded and recorded into the patient's clinical notes and the date the form was completed should be documented. It is strongly suggested the date the RAF was completed is annotated in the script notes of any prescribed valproate so it can be easily identified. If the RAF has not been completed by the specialist, this must be referred to secondary care without delay to reduce the risk of the patient experiencing delays in treatment.

The following read codes should be used:

- Valid Risk Assessment completed: Valproate Annual Risk Acknowledgement "Form completed" SCTID: 1366401000000107 (SystmOne *Y362e*)

- Referral made for completion of risk assessment: "Referral for completion of" Valproate Annual Risk Acknowledgement Form SCTID: 1366381000000107 (SystmOne Y38a6)

The prescribing clinician must be satisfied that the RAF has been fully completed for males of fathering potential initiated on valproate since January 2024 prior to issuing any prescriptions for valproate. If there is any doubt it is the responsibility of the clinician signing the prescription to review and, where necessary discuss with the patient.

Male patients prescribed valproate must be offered an annual medication review with appropriate monitoring undertaken,

2.81 Males under 55 years with existing valproate prescription.

The most recent MHRA alert only stipulates new male patient under the age of 55 years must have a RAF completed. Although it is anticipated this position will likely change in the near future, no further action is required in this group of patients. However, due to the risks of fertility and testicular toxicity, any male presenting with plans to start a family should be referred to a specialist for further advice.

All male patients prescribed valproate should be offered an annual medication review with appropriate monitoring undertaken.

3.0 Specialist Responsibilities

The responsibilities of the specialist are outlined in the local formulary decision for valproate. All NHS Trusts within NWICB involved in the prescribing of Valproate must have their own prescribing guidance in place to ensure adherence to the 2023 MHRA patient safety alert.

3.1 Women with childbearing potential

The Specialist must ensure all women of childbearing potential prescribed valproate are reviewed at **least annually.**

3.11 The next annual review

At the patient's next annual review, the specialist is responsible for reviewing the valproate and confirming it is still the most appropriate treatment. Where appropriate the risks of pregnancy must be fully discussed to enable the patient to make an informed decision regarding the continued prescribing of valproate. The ARAF must then be completed with a countersignature obtained by a relevant clinician as outlined by the Trust's valproate prescribing guidance. Copies of the completed ARAF must be sent to the GP practice, the patient and a copy retained in the patient's notes.

Where the patient is not currently using highly effective contraception, this must be discussed with the patient with signposting to appropriate services which can offer this. The GP should also be made aware highly effective contraception is not in use. Without the use of highly effective contraception, prescribing of valproate in women of childbearing potential becomes unlicensed and therefore prescribing of valproate may need to remain with the specialist until appropriate contraception is initiated. This must be considered on an individual patient basis with the risk of pregnancy considered.

3.12 Subsequent annual review

At all subsequent annual reviews, the risks and benefits of continued valproate must be reviewed and discussed with the patient. Where valproate prescribing is to continue, the ARAF form will need to be completed however the secondary signatory is not required.

3.2 Women without childbearing potential or those currently exempt from PREVENT

The most recent MHRA guidance stipulates **all women under the age of 55 years** must have a new ARAF completed by two independent specialists. Some of these female patients may no longer be under specialist care or may have previously had a one-off ARAF form completed.

3.21 The next annual review

In order to comply with the alert, this cohort of women will be required to be reviewed by a specialist to have an updated ARAF completed alongside a secondary signatory. In some cases, for example where there is permanently no risk of pregnancy, it may be appropriate to complete the ARAF as a one-off and, provided her condition is stable, may be discharged from secondary care. This decision must be clearly documented on the ARAF. Where there remains a risk of pregnancy, the specialist must continue to review these patients at least annually.

3.3 Female patients who do not meet criteria of PREVENT

Prescribing of valproate where the conditions of PREVENT are not met represents an unlicensed use of the drug. The prescribing of valproate must be carefully considered and where valproate is deemed the only suitable option, it is strongly suggested that the individual case is discussed with the senior consultant. Consideration should also be taken as to whether to discuss with the Clinical Director as there may be implications on the Trust in any future pregnancies resulting in harm to the baby.

It may be appropriate to consider additional resources, for example best interest meetings (where the patient lacks capacity) or a multidisciplinary team meeting to facilitate decision making. It is important the patient/carer is fully involved in these discussions (where appropriate) so she is fully involved and can make an informed decision about treatment. All discussions must be documented.

The ARAF must be completed clearly stating the conditions of PREVENT have not been met. Copies of the form must be held in the patient's notes, sent to the GP surgery and given to the patient. Folic acid 5mg tablets must also be prescribed to minimise risks should the women become pregnant.

Whilst the conditions of PREVENT are not met, the prescribing of valproate should remain with the specialist. The women must be informed of this as this may factor into her decision-making process. Once the conditions of PREVENT have been met, prescribing of valproate can be transferred to primary care. This decision must be clearly documented on the ARAF.

3.4 Women who become pregnant whilst taking valproate

Any women prescribed valproate who becomes pregnant must be urgently referred to her specialist. She must be reviewed within days and the ongoing prescribing of valproate reviewed. The risks to her unborn baby due to continuing valproate must be discussed and clearly documented in her notes. If the decision is made to continue prescribing valproate throughout her pregnancy, the prescribing must remain with the specialist. The Trust's Clinical Director must be notified of the situation. Any decisions must be clearly documented in her notes.

3.5 Men prescribed valproate

Due to emerging evidence of potential risks of impaired male fertility and possible transgenerational neurodevelopmental effects, any new males under the age of 55 years must have a one-off RAF completed by their specialist and countersigned be an appropriate secondary signatory.

The risks versus benefits, including those risks of fathering a child, must be discussed so the patient is able to make an informed decision regarding valproate care. Patients must be informed to consult with their GP or specialist prior to planning a family.

Where a male under the age of 55 years presents to discuss plans to start a family, he must be referred to the specialist for review and advice.

4.0 Sexual Health Clinics responsibilities

The sexual health clinic will support female patients of childbearing potential with advice and initiation, and continuation of appropriate contraception. Referrals to the service can be made via primary or secondary care (Appendix 2) or via direct patient referral.

To ensure the patient is prioritised for treatment, referrals from Healthcare Professionals should provide full details on valproate prescribing. Incomplete referral forms may lead to delays in treatment.

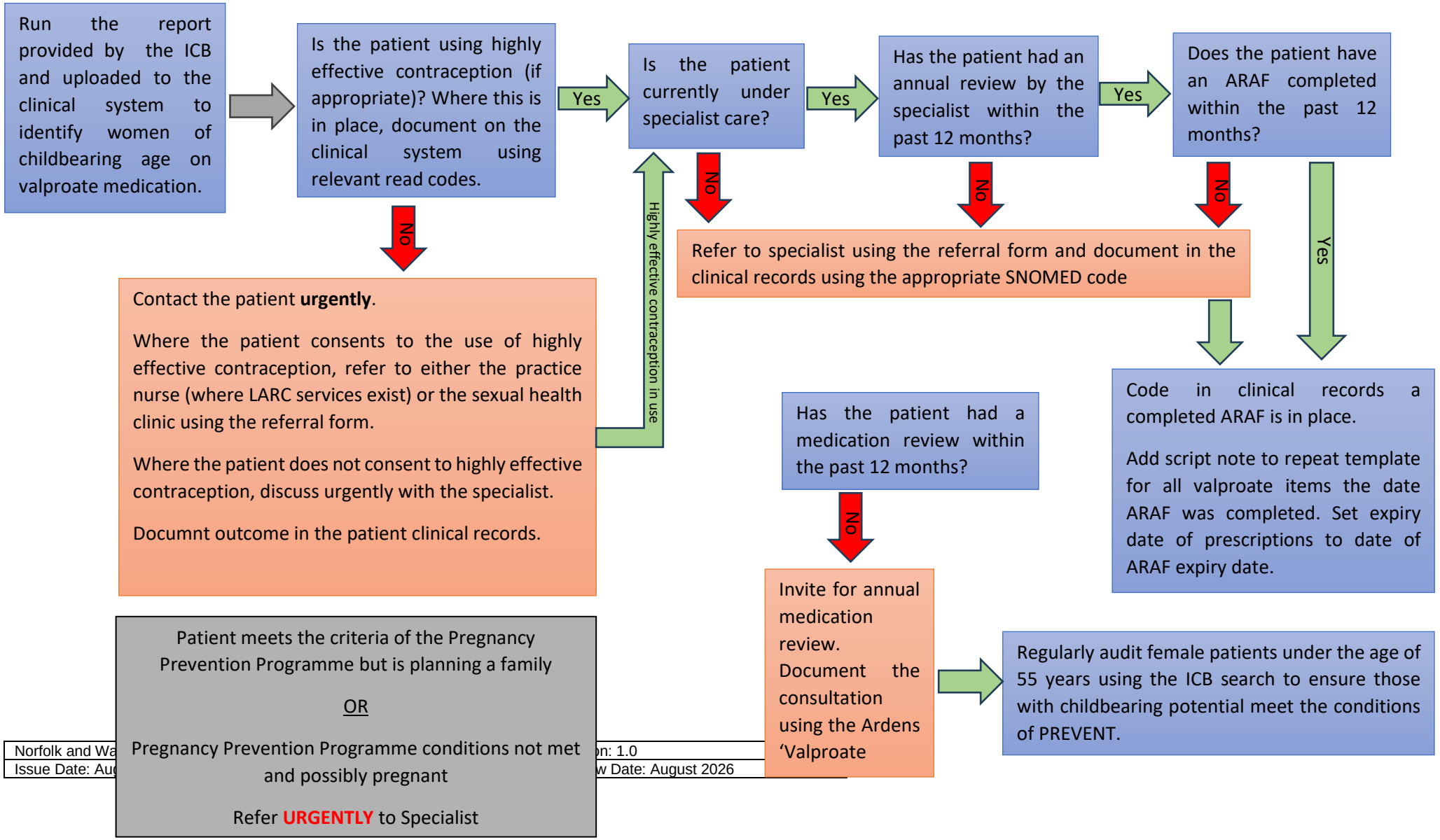
The clinic will undertake a detailed history of the patient and will discuss the risks of valproate treatment in pregnancy. Patients will be actively involved in discussions as to the most appropriate method of contraception method for them.

Once contraception has been initiated, consent from the patient will be sought by the clinic to inform the referring clinician of what contraception is in place. In the event of referral from secondary care, the GP surgery will also be notified provided the patient consents and details have been provided.

If the patient refuses highly effective contraception, or requests removal of LARC, with patient consent the clinic will notify the GP and/or specialist where known.

In some circumstances, the sexual health clinic may need to refer to secondary care for initiation for insertion/removal of highly effective contraception should the procedure not be considered safe to undertake in the community setting.

7.0 Appendix 1 - Referral flow diagram: existing female patients under 55 years prescribed valproate



8.0 Appendix 2 - Primary Care Referral Form

GP Referral Form for Annual Review of Women and Girls of Childbearing Potential taking Valproate*

This referral form is for any woman or girl of child-bearing potential (aged 11-54 years) currently prescribed valproate for either a mental health condition or epilepsy. Prescribing advice for other indications will need to be sent directly to the clinician who initiated valproate.

Please send completed referrals to the following:

Norfolk and Norwich University Hospitals NHS Foundation Trusts • Via electronic referral
James Paget University Hospitals NHS Foundation Trust • Via electronic referral
Queen Elizabeth Hospital Kings Lynn NHS Foundation Trust • Via electronic referral
Norfolk and Suffolk NHS Foundation Trust • valproateadmin@nsft.nhs.uk

Valproate should only be prescribed in women and girls of childbearing potential if the conditions of the PREVENT pregnancy prevention programme (PPP) are met. This includes having a completed Annual Risk Assessment Form (ARAF) and highly effective contraception in place. In 2023 the MHRA issued a new patient safety update stating that women of child-bearing potential under the age of 55 years must have the subsequent ARAF form signed by two independent specialists to be completed at their next annual review.

Valproate should not be stopped abruptly, but consideration will need to be given to the suitability of valproate treatment if the requirements of the PPP cannot be met.

*Brand names include, Epilim®, Depakote®, Convulex®, Episenta®, Epival®, Kentlim®, Orlept®, Syonell®, Valpal®, Belvo® & Dyzantil®. Other names used to describe valproate containing medicines are sodium valproate, valproic acid, and semisodium valproate.

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Patient Name: Full Name	Patient date of Birth: Date of Birth
NHS number: NHS Number	
Patient Address: Home Full Address (stacked)	
Patient telephone number: Patient Mobile Telephone	
Parent/carer name:	Relationship to patient:
Parent/carer address:	
Parent/carer telephone number:	
Name of referrer: Usual GP Full Name	Date of referral: Short date letter merged
Address: Usual GP Full Address (single line) Telephone: Usual GP Phone Number Email:	
GP contact details: Usual GP Full Name Usual GP Full Address (stacked)	
Interpreter required: ☐ YES ☐ NO Language:	
Disability (including a Learning Disability): ☐ YES ☐ NO if yes please specify:	

* Throughout this document the terminology used is that given by the MHRA. All practitioners treating people taking valproate should be mindful that some individuals who do not identify as female may be of childbearing potential.

Section 1 – Please complete for ALL referrals	
1. Is the patient already under specialist services?	☐ Yes ☐ No

Section 1 – Complete only if the patient is pregnant or planning a pregnancy	
1. Is the patient pregnant or planning pregnancy?	☐ Planning a pregnancy ☐ Pregnant Gestation?

Section 2 – Complete only if the referral is related to an ARAF	
2. Is the referral for completion of a valproate ARAF?	☐ Yes ☐ No
3. Does the patient have a current valproate ARAF completed within the last 12 months by the specialist?	☐ Yes ☐ No

Section 3 – for ALL referrals please complete as much as possible	
4. What is the indication for use of valproate?	☐ Bipolar ☐ Epilepsy ☐ Bipolar and Epilepsy (referral to be sent from initiating speciality)

5. Dose, preparation and brand (where applicable) of valproate prescribed	
6. Is the patient currently exempt from PREVENT?	☐ Yes Reason ☐ No ☐ Unsure
7. Are there any reasons to indicate there is no risk of future pregnancy? *This may include, but not exhaustive: infertility, menopause, transgender, sterilisation etc.* *Learning disabilities do not automatically exclude the patient from the PREVENT programme.* **The final decision on exemption remains with the specialist**	☐ Yes Details ☐ No
8. Have any mental capacity issues related to capacity or consent regarding medication/contraception been identified?	☐ Yes Details ☐ No

9. Is the patient using highly effective contraceptive? *This information must be included to process the referral. If you are unsure of contraception status, please contact the patient to discuss. If highly effective contraceptive is not in use, please review the patient as a matter of urgency. Referrals cannot be accepted without this information.*

☐ Yes (please indicate in list below)

☐ No

- ☐ Patient referred on (date):
- ☐ Patient refuses

Highly effective contraception is considered for regulatory purposes to be those user independent methods:

☐ Copper intrauterine device (Cu-IUD)

☐ Levonorgestrel intrauterine system (LNG-IUS)

☐ Progestogen only implant (ENG-IMP)

☐ Progestogen-only injection administered on schedule by a healthcare professional

☐ Female sterilisation

What contraceptive arrangements are in place if not using a highly effective contraceptive? *User dependent methods are not considered highly effective such as the condom, cap, diaphragm, self-administered progestogen-only injections, combined oral contraceptive pill (COC) or progestogen-only contraceptive pill (POP) and fertility awareness-based methods.*

All forms of CHC, including rings and patches, or POP methods have a typical failure rate of around 9% and must be used together with a barrier method of contraception with frequent pregnancy testing carried out.

Contraception method(s):

10. All currently prescribed medication, including doses:	
11. Allergies:	☐ Yes please specify: ☐ No

Links and further information

- More information relating to the national MHRA alert can be found here: National Patient Safety Alert: Valproate: organisations to prepare for new regulatory measures for oversight of prescribing to new patients and existing female patients (NatPSA/2023/013/MHRA) - GOV.UK (www.gov.uk)
- Patient and Professional resources: Valproate use by women and girls - GOV.UK (www.gov.uk)
- For other valproate information including brand names* visit: https://www.nhs.uk/medicines/sodium-valproate/

9.0 Appendix 3 - Sexual Health Referral Form

Referral Form for initiation of contraception by the sexual health service for women taking Valproate*

This referral form is for primary and secondary care use for the referral of woman or girls of child-bearing potential (aged 11-55yrs) prescribed valproate who require initiation of highly effective contraception by their local sexual health clinic.

Referrals will only be accepted with a fully completed referral form. Please send completed referrals to the following:

Norfolk • **Norwich:** CCS-TR.icashnorwich@nhs.net • **Great Yarmouth:** CCS-TR.BreydonClinicReferrals@nhs.net • **Kings Lynn:** ccs-tr.icashkingslynn@nhs.net
Waveney • **Lowestoft:** provide.regentroad@nhs.net

*Brand names include, Epilim®, Depakote®, Convulex®, Episenta®, Epival®, Kentlim®, Orlept®, Syonell®, Valpal®, Belvo® & Dyzantil®. Other names used to describe valproate containing medicines are sodium valproate, valproic acid, and semisodium valproate.

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Patient Details	
Patient Name: Full Name	Patient date of Birth: Date of Birth
Patient Address: Home Full Address (stacked)	
Patient telephone number: Patient Mobile Telephone	
Parent/carer name:	Relationship to patient:
Parent/carer address:	
Who is the preferred point of contact? Preferred contact telephone number:	
Interpreter required: ☐ YES ☐ NO Language:	
Disability (including a Learning Disability): ☐ YES ☐ NO if yes please specify:	

Referrer details	
Primary care: ☐ Secondary Care ☐	
Name of referrer: Usual GP Full Name	Date of referral:
Address: Usual GP Full Address (single line) Telephone: Usual GP Phone Number Email:	

GP Contact details
GP contact details: Usual GP Full Name Usual GP Full Address (stacked)

Secondary Care details (to be completed when referral sent by secondary care)
Clinician contact details: Name Address: Telephone: Email: Clinic:

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Norfolk and Waveney Integrated Care System

Section 1: To be completed by the referrer

* Throughout this document the terminology used is that given by the MHRA. All practitioners treating people taking valproate should be mindful that some individuals who do not identify as female may be of childbearing potential.

Please complete all boxes. Forms which have not been completed fully will not be accepted

1. Is there any imminent risk of unintended pregnancy?	☐ **Yes** ☐ **No**
2. What is the patient's age?	

3. What is the indication for use of valproate in this patient?

☐ Bipolar ☐ Migraine
☐ Epilepsy ☐ Other, please specify

4. What is the dose and brand / preparation of valproate prescribed:

5. Is the patient currently under specialist care?

☐ Yes – please specify below
- ☐ Norfolk and Norwich University Hospitals NHS Foundation Trusts
- ☐ James Paget University Hospitals NHS Foundation Trust
- ☐ Queen Elizabeth Hospital Kings Lynn NHS Foundation Trust
- ☐ Norfolk and Suffolk NHS Trust
- ☐ Norfolk Community Health and Care NHS Trust

☐ No

6. What is the current method of contraception?
It is very important this information is included to process the referral. If you are unsure of contraception status, please contact the patient to discuss. Referrals cannot be accepted without this information.

☐ None
☐ Copper intrauterine device (Cu-IUD)
☐ Levonorgestrel intrauterine device (LNG-IUD)
☐ Progestogen only implant (ENG-IMP)
☐ Progestogen-only injection administered on schedule by a healthcare professional
☐ Combined oral contraceptive pill ☐ ring ☐ patch ☐
☐ Progesterone only contraceptive pill
☐ Barrier methods
☐ Natural family planning
☐ Male sterilisation

7. Are there any compelling reasons to indicate that there is no risk of pregnancy? If yes, please provide details (please note, learning disabilities do not automatically exclude the patient from the PREVENT programme)

☐ No
☐ Yes Please give details

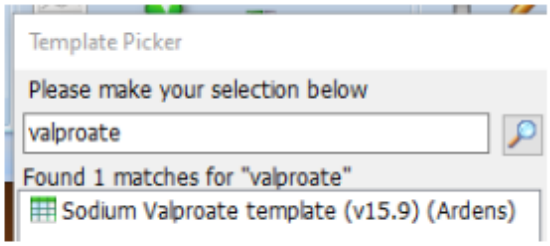
8. Have any mental capacity issues related to capacity or consent to medications/contraception been identified? ☐ Yes Please give details ☐ No (Please provide carers details where appropriate)
9. If blood results available, please detail below: Single Code Entry: LFT - Liver function test Single Code Entry: FBC - full blood count
10. All currently prescribed medication, including doses: Medication
11. Any relevant medical history, including BMI:
12. Allergies: ☐ Yes ☐ No If yes please specify:
13. Any other relevant details e.g. accessibility issues, uncontrolled seizures?

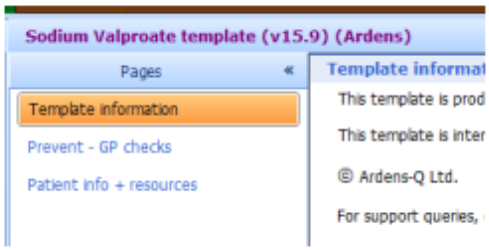
Links and further information

- More information relating to the national MHRA alert can be found here: National Patient Safety Alert: Valproate: organisations to prepare for new regulatory measures for oversight of prescribing to new patients and existing female patients (NatPSA/2023/013/MHRA) - GOV.UK (www.gov.uk)
- Patient and Professional resources: Valproate use by women and girls - GOV.UK (www.gov.uk)
- For other valproate information including brand names* visit: https://www.nhs.uk/medicines/sodium-valproate/

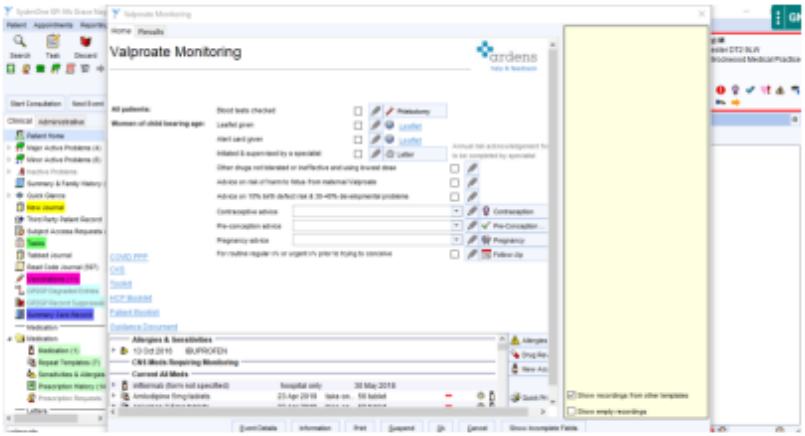
10.0 Appendix 4 – Ardens template screen shots on EMIS and SystmOne

EMIS





SystmOne



11.0 Appendix 5: Valproate prescribing in Primary Care – Frequently Asked Questions.

All healthcare professionals involved in the prescribing or monitoring of valproate must be familiar with the 2023 MHRA alert for valproate and have read the 'Guide for Healthcare Professionals'

When can primary care start female referring patients who require review?

The ICB is the final stages of confirming the referral processes which each of the four trusts where valproate prescribing occurs. We have taken time to establish this process to ensure it is robust and all patients that need to be referred are done so in a safe manner and to allow triaging by secondary care according to need.

What will be the process of referral?

To aid this process we have developed new guidance for referrals and referral forms for primary care. These are awaiting final sign-off and will be shared with you once this has been completed. For now, please continue to withhold from referring any patients requiring review. We anticipate secondary care will be able to accept referrals from mid to late May but will inform you all as soon as this is possible.

How will patients be prioritised?

Those female patients under the age of 55 years who will require referral to secondary care are as follows:

- Those not currently under specialist care (including those who may have previously been discharged)
- Those patients without an ARAF from completed by a specialist within the past 12 months.

Patients who are under secondary care and have had a review and a completed ARAF within the past 12 months **will not** need a referral as they should have a planned annual review where the ARAF form will be completed by two specialists.

Are GP practices able to complete the ARAF?

Some surgeries have asked whether they can complete any incomplete or out of date ARAFs. The MHRA update specifically states these must be completed by the specialist and countersigned by an appropriate secondary signature with relevant expertise. The ICB would not encourage the completion of ARAFs in primary care.

Where it has been identified that a patient does not have a current ARAF, this may be documented in the patient clinical records to acknowledge the missing documentation. The practice should keep an updated list of those patients currently not adhering to the MHRA alert.

What can the surgery do to prepare before referral?

Where it has been identified a referral to a specialist is required, the practice may wish to start planning how discussions with these patients will take place. Patients should be informed of the need to refer and this may require an appointment.

Where a patient has been identified as not having highly effective contraception in place, the patient should be invited for a consultation to discuss further and, where necessary referred to the sexual health clinic or an appointment made with the practice nurse where LARC is available.

How can I document my consultations?

Robust documentation and read code is vital following a consultation with a women of childbearing potential prescribed valproate. Where Ardens templates are available the ICB strongly recommends the use of 'Valproate Monitoring'.

The following SystmOne and SNOMED codes are also recommended:

	SystmOne code	SNOMED Concept ID
Pregnancy Prevention Programme started *To be used when an ARAF is received from secondary care and ongoing annual reviews are required*	Y2f16	1129771000000103
Pregnancy Prevention Programme declined *To be used the patient has been referred to secondary care, was given an appointment for ARAF completion but did not attend*	Y2f17	1129801000000100
Pregnancy Prevention Programme not needed *To be used when an ARAF is received from secondary care and ongoing annual reviews are not needed, for example, a patient who is of childbearing age but has had a hysterectomy*	Y2f18	1129791000000104
Pregnancy Prevention Programme discontinued	Y2f19	1129841000000102
Did not attend Pregnancy Prevention Programme	Y2f1a	1129831000000106
Pregnancy Prevention Programme declined by parent	Y2f1b	1129821000000109
Pregnancy Prevention Programme declined caregiver	Y2f1c	1129811000000103
Valproate Annual Risk Acknowledgement Form completed *To be used when Valproate ARAF received from secondary care*	Y362e	1366401000000107
Referral for completion of Valproate Annual Risk Acknowledgement Form *To be used when a referral has been made from primary care to secondary care*	Y38a6	1366381000000107

My patient is currently exempt from the Pregnancy Prevention Programme, do they need an updated ARAF?

All female patients under the age of 55 years will require an updated ARAF which ahs been signed by two specialists. This includes patients that are currently exempt from the pregnancy prevention programme or who may have had a one-off form completed. We understand that this may mean some patients potentially having to have difficult conversations but we hope this can be avoided by detailing reasons for exemption on the referral form.

My patient is refusing referral to secondary care, what should I do?

Valproate is unlicensed for women under the age of 55 with childbearing potential if the conditions of the pregnancy prevention programme is not met. Patients should be strongly encouraged to attend appointments with the specialists to ensure they are receiving appropriate care.

On an individual prescriber level this might mean they may not be able to meet the GMC's professional standard expectations, which can be found in both Good Medical Practice and Good Prescribing Practice or equivalent for non-medical prescribers.

The ICB is currently reviewing the formulary status of valproate products to support primary care when potentially face with this scenario.

My patient is not currently using highly effective contraception, what should I do?

The need for highly effective contraception must be discussed with the patient and, where appropriate and consented to, a referral should be made to the sexual health clinic for initiation or where LARC is available within a practice, an appointment made with the practice nurse as a matter of urgency.

Where the condition of the pregnancy prevention programme are not met, the prescribing of valproate in epilepsy and bipolar become unlicensed.

The ICB is currently reviewing the formulary status of valproate products to support primary care when potentially face with this scenario.

My patient is pregnant or wishes to start a family, can I continue valproate prescribing?

If a female patient prescribed valproate confirms they are pregnant an urgent referral must be made to her specialist. She should be reviewed within 5 days. She must be reminded **not to stop valproate treatment.** Valproate is **contra-indicated in pregnancy** for the treatment of bipolar. It is also contra-indicated in epilepsy unless two specialists independently review and consider it as the only suitable treatment option.

For females expressing a desire to start a family, she should be referred to her specialist for advice. She should be reminder to **continue her contraception and not stop valproate treatment** and also of the risks valproate may have on her unborn baby (congenital malformations and neurodevelopmental delays). This discussion must be clearly documented in her clinical record.

For males prescribed valproate who wish to start a family within the next 12 months, they should be referred to their specialist. This is due to potential risks of valproate affecting fertility but also possible testicular toxicity. The patient should be reminded not to stop their valproate treatment and to continue using contraception until advice from the specialist is sought.

How should I manage a patient who had valproate initiated by primary care?

Valproate is only licensed for the use in epilepsy and bipolar. For patients where valproate was initiated in primary care for either of these indications, a new referral will be required to secondary care.

Women under the age of 55 years with childbearing potential who had valproate initiated in primary care for any other indication **must** be reviewed. There should be a discussion on stopping treatment. The ICB is currently reviewing formulary status.

My patient is prescribed valproate for an indication other than epilepsy or bipolar which was initiated by secondary care, how should this be managed?

Prescribing of valproate for women of childbearing potential for any other condition other than epilepsy or bipolar is unlicensed. These patients should be referred to the clinician / clinic who commenced treatment.

The ICB recognises there are a small number of patients prescribed valproate for migraines, this is unlicensed and therefore the specialist who initiated treatment should review the patient with a view to switching to an alternative treatment.

The ICB is currently reviewing the formulary status of valproate products to support primary care when potentially face with this scenario.

The latest MHRA alert mentions male patients under the age of 55 years, do I need to do anything about this group of patients?

The alert stipulates that any male under the age of 55 years **newly initiated** on valproate must have a risk assessment form completed by two specialists. This is a one-off form and does not need to be completed annually. On receiving the form, this must be uploaded into the patient's clinical record and recoded using the read codes above.

The ICB also strongly suggests adding a script note to valproate prescriptions on the repeat template with the date the RAF was signed so it is easily identifiable that this has been completed.

In the event a male patient under the age off 55 years is started on valproate and has not received a RAF, this should be referred back to secondary care and the ICB Medicines Optimisation Team notified.

For male patients under the age of 55 years with an existing valproate prescription, no further action is required unless the patient expresses plans to start a family within the next 12 months. In these circumstances the patient should be referred to the specialist for advice. **The patient must be reminded not to stop valproate treatment.**

My patient has been reviewed by secondary care, what steps do I need to take?

Once the ARAF has been received, this should be uploaded into the patient's clinical record and recoded as per the recodes above. It is also suggested that the date the ARAF was completed is added to all valproate repeat templates as a script note so it is quickly visible when prescriptions are requested. Where the patient is exempt from the pregnancy prevention programme this must also be appropriately read coded.

Patients should be invited for a consultation with an appropriate healthcare professional. The clinician should check there is a valid ARAF and ensure the patient has been provided with the patient information leaflet.

For women of childbearing potential there must be a discussion of the risks of pregnancy (congenital malformations and neuro-developmental delay) whilst prescribed valproate and to ensure she understands the need to use highly effective contraception. Where Ardens is available, the 'Valproate monitoring' template should be used. She should be reminded never to stop treatment without advice from the specialist and what to do if she becomes pregnant or wishes to start a family.

What ongoing actions does the practice need to undertake to ensure we are compliant with the alert monitoring?

CQC may request evidence from the practice for assurances that this alert has been actioned and continues to be managed to ensure the safety of patients. Practices 'must do all that is reasonably practicable to mitigate risks'.

The ICB has developed some searches to enable practices to identify those female patients under the age of 55 years prescribed valproate. It is strongly suggested this search is run monthly to ensure all patients meet the requirements of the alert. Where requirements are not met, the practice must take action, i.e. referral to specialist, to mitigate the risks. This process must be documented and accessible to staff responsible for overseeing this process.

The practice should have a robust recall system in place to ensure patients prescribed valproate are offered an annual medication review.

Who can I contact for further advice or to raise an issue?

If you have any questions or need advice regarding this alert, please contact the ICB via email nwicb.medsqueries@nhs.net

If the practice has any concerns, for example not receiving a completed ARAF from secondary care, please inform us via the same address.

12.0 References

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2. Medicines and Healthcare products Regulatory Agency. National Patient Safety Alert: Valproate: organisations to prepare for new regulatory measures for the oversight of prescribing to new patients and existing female patients. November 2023. 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#:~:text=Valproate%20must%20not%20be%20started,reproductive%20risks%20do%20not%20apply. (accessed 21/02/24)

3. Medicines and Healthcare products Regulatory Agency. Valproate use by women and girls. Information about the risks of taking valproate medicines during pregnancy. March 2018. https://www.gov.uk/guidance/valproate-use-by-women-and-girls#:~:text=Since%202018%20any%20use%20of,need%20to%20avoid%20becoming%20pregnant (accessed 21/02/24)

4. Medicines and Healthcare products Regulatory Agency. Guide for Healthcare Professionals. Information on the risks of Valproate use in all patients. December 2023. https://mhra-gov.filecamp.com/s/i/eGygqKVE00FH393c (accessed 28/03/24)

5. Medicines and Healthcare products Regulatory Agency. Medicines with teratogenic potential: what is effective contraception and how often is pregnancy testing needed?. March 2019. https://www.gov.uk/drug-safety-update/medicines-with-teratogenic-potential-what-is-effective-contraception-and-how-often-is-pregnancy-testing-needed (accessed 29/02/24)

6. Medicines and Healthcare products Regulatory Agency. Valproate safety measures. Risk Acknowledgement Form for female patients: Valproate has risks in pregnancy. December 2023. https://mhra-gov.filecamp.com/s/i/6iqrRqc0zoFgeEo7 (accessed 28/03/24)

7. Medicines and Healthcare products Regulatory Agency. Valproate safety measures. Risk Acknowledgement Form: For Male Patients Starting Valproate. December 2023. https://mhra-gov.filecamp.com/s/i/bEnPD49yZtHsXp3M (accessed 29/02/24)

8. Medicines and Healthcare products Regulatory Agency. Full pack dispensing of valproate-containing medicines. October 2023. https://www.gov.uk/government/publications/full-pack-dispensing-of-valproate-containing-medicines/full-pack-dispensing-of-valproate-containing-medicines (accessed 22/02/24)

9. Specialist Pharmacy Service. Valproic acid and sodium valproate monitoring. July 2021. https://www.sps.nhs.uk/monitorings/valproic-acid-and-sodium-valproate-monitoring/ (accessed 02/04/24)

10. NHS England. Network Contract DES: Contract specification 2024/25 – PCN requirements and entitlements (accessed 02/04/24)