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Integrated Care Board

Valproate Safety Update

BSW Medicines Optimisation Team

Wednesday 17th of April 2024

Please get in touch if you'd like to be involved in valproate safety improvement work with the ICS bswicb.prescribing@nhs.net

Agenda

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- Background: MHRA, NatPSA Alert, CMO letter & National Medication Safety Improvement Programme (MedSIP)
- BSW Together Valproate Safety Group
- Risks of valproate
- Existing & NEW MHRA Regulatory Measures
- Resources for Patients and Healthcare Professional
- BSW Primary Care Valproate Audit Findings – Prescirbing Quality Incentive Scheme 2022/23
- Contraception for women - Valproate Pregnancy Prevention Programme
- Actions for GP Practices

Background

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- MHRA are concerned that the regulatory requirements for safe use of valproate are not being consistently followed.
- Nationally pregnancies continue to be exposed to valproate (53 in the last year).
- Emerging evidence of potential reproductive risks in males.
- MHRA recommend new regulatory safety measures. Phase 1 January 2024. Phase 2 to follow later in 2024. GOV Valproate Safety
- National Patient Safety Alert November 2023: Valproate: New Regulatory Measures new patients (male and female) and existing female patients. 'Phase 1'. ICB to co -ordinate an ICS Valproate Safety Group with key stakeholders (specialists from relevant disciplines & general practice) https://www.cas.mhra.gov.uk/NatPSA Valproate
- Chief Medical Officer letter https://www.cas.mhra.gov.uk/CMO Valproate Safety Message

Valproate safety included as National MedSIP priority. The Valproate Integrated Quality Improvement programme launched in November 2023. Aims to:

- Support Integrated Care Boards to make the use of Valproate as safe as possible.
- Eliminate the harm Valproate causes to babies in the womb, while providing the best possible *personalised care* for patients and preventing deaths from epilepsy and/or bipolar disorders.
- The programme has so far seen a 35% reduction in number of women of childbearing age prescribed Valproate.

No one should stop taking valproate without advice from a specialist due to the serious risks associated with worsening control of epilepsy or bipolar disorder

BSW Together Valproate Safety Group Update

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BSW Together Valproate Safety Working Group

BSW Valproate Safety Working Group established in January 2024, with stakeholders from partner organisation, including clinical leads in neurology, mental health, paediatrics, contraception and sexual health, learning disability, general practice and medication safety teams. Medical, nursing and pharmacy professionals.

Working Group Improvement Themes

The group identified themes for improvement:

- **All Partner Organisations to review internal procedures for valproate safety measures.** Document internal 'procedure' for the new and existing valproate regulatory measures [including Pregnancy Prevention Programme (PPP), Annual Risk Acknowledgement Form (ARAF), Risk Acknowledgement Form (RAF) (new males)]. Include defined roles and responsibilities and the secondary independent signatory arrangement at both inpatients and outpatient setting.
- **A system Share Care Agreement and role & responsibility document**. To clearly define role and responsibility for safe valproate prescribing & facilitate transfer of care.
- **Data validation of registers. Digital Tools to empower** specialist team colleagues to hold an up-to-date registers and proactively recalling patients for annual review and communicate risk acknowledgement forms across pathways. Minimise administrative burden of referral arrangements.
- **Highly effective contraception.** Focus on education and clarification of the contraception pathways/choices/approach.
- **Learning Disability Inequalities**. Mapping exercise to establish the current pathway and resources available.

Challenges

- Multiple organisations and teams involved in the valproate prescribing pathway. Communication at transfer of care/interface.
- No easy digital solution for signing and returning of ARAF forms to all providers. Lack of comprehensive system wide transfer of information.
- Provider colleagues' capacity to undertake the new MHRA dual specialist sign off and include male patients.
- Decision and communication of whether a patient has a permanent absence of risk in relation to pregnancy. This would include situations where patient has a changing level of capacity.

Assessment

Prevalence

- BSW prescribing data indicates 70% of patients prescribed valproate is for epilepsy & 30% for mental health conditions.
- Prevalence of female at childbearing age on valproate is 4 per 10,000 registered patients, while male is 10 per 10,000 registered patients.
- Our prevalent male valproate population is approx. 2.5 males to every 1 women, which is lower than national average 4:1.
- Despite the small number of patients prescribed valproate in BSW, the lifetime cost of one baby born with valproate is significant to individual/family/system

Learning and development problems	Physical disabilities
Autism £ 2,409,000	Spina bifida £927,000
ADHD £124,000	

These costs are incurred by the affected families, the NHS, the education system, the welfare system and wider society.

Inequality

- Approx. 1/5 of patients (female and male) prescribed valproate also have learning disability read coded.
- No strong correlation between index of multiple deprivation (IMD) and valproate prescribing in women observed in practice level.

Risks of Valproate

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Risks of Valproate in Women

Highly teratogenic.

Exposure in utero leads to physical birth defects in 11% of babies and neurodevelopmental disorders in up to 30-40%. Foetal valproate syndrome.

All women and girls of *childbearing potential* being treated with valproate must be supported on a Pregnancy Prevention Programme (PPP)
https://www.gov.uk/guidance/valproate-use-by-women-and-girls

Reference MHRA Public assessment report: GOV Valproate Safety

Risks of Valproate in Men

May cause infertility.

Toxic effects on the testes have been observed in animals - unclear what it means for humans.

Data currently being analysed by MHRA *may* suggest an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception. Around 5% children born to fathers treated with valproate around conception were diagnosed with a neurodevelopmental disorder compared to 3% in children whose fathers were taking lamotrigine or levetiracetam (two other anti-seizure medicines).

As a precaution male patients on valproate who are planning a family within the next year should speak to a healthcare professional about their treatment options.
January 2024 Drug Safety Update

Existing & NEW MHRA Regulatory Measures – required when prescribing valproate

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Existing Measures

All ***women*** and ***girls of childbearing potential*** being treated with valproate medicines must be supported on a **Pregnancy Prevention Programme** (PPP) unless the prescriber considers that there are *compelling reasons to indicate that there is no risk of pregnancy*.

The PPP includes a set of conditions to ensure all female patients taking valproate:

- See their specialist at least every year
- Have been informed and understand the risks of use in pregnancy and have signed an Annual Risk Acknowledgement Form (ARAF)
- Are prescribed highly effective contraception as appropriate

See MHRA Valproate Pregnancy Prevention Programme

NEW Measures from Jan 2024 (Phase 1)

NOTE: Phase 2 Measures *(to cover existing male patients) are expected later in 2024*

- New Regulatory Measures from January 2024:
  - Valproate must not be started in new patients (**male or female**) younger than 55 years, unless two specialists independently consider and document that there is **no other effective or tolerated treatment**, or there are compelling reasons that the reproductive risks do not apply.
  - At their next annual specialist review, **women** of childbearing potential and girls should be reviewed using a revised valproate Risk Acknowledgement Form, which will include the need for a second specialist signature if the patient is to continue with valproate and subsequent annual reviews with one specialist unless the patient's situation changes

New Male Risk Acknowledgement Form for any new initiations of valproate in *males*
Annual Risk Acknowledgement Form for females updated

Resources for patients and healthcare professional

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Resources for patients and healthcare professional

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

- Patient guide: Provides those taking valproate (or their parent, caregiver, or responsible person) with information on the risks of valproate in pregnancy and the risks to male patients and what they need to do.
- 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.
- Annual Risk Acknowledgement Form: For female patients starting valproate and at annual review. Used to support and record the discussion between the patient and **specialist** prescriber on the risks associated with valproate in pregnancy and to record the decision of the countersigning specialist. At subsequent annual reviews only one specialist is required.
- Risk Acknowledgement Form for male patients starting valproate: Used to support and record the discussion between the patient and **specialist** prescriber of the risks associated with valproate in males when starting treatment with valproate and to record the decision of the countersigning specialist. This is only to be completed at initiation of valproate.
- Patient card: Provides key information for female patients receiving valproate on contraception and pregnancy prevention.
- Pharmacy poster: Provides important actions for pharmacists dispensing valproate to female patients.
- Warning stickers: To be added to packaging of medicine in exceptional circumstances where the original pack cannot be dispensed.

See Product Information for valproate medicines, including the Patient Information Leaflet.

Information should be provided in an accessible format where necessary, for example easy read, other languages.
https://www.choiceandmedication.org/awp/printable-leaflets/patient-information-leaflets/139/ALL/ Decision Support Tools. To be used by specialist neurology or psychiatry teams to reach shared decisions about how appropriate valproate treatment is for this as an individual.
https://www.england.nhs.uk/publication/decision-support-tool-is-valproate-the-right-epilepsy-treatment-for-me/ &
https://www.england.nhs.uk/publication/decision-support-tool-bipolar-disorder-is-valproate-the-right-treatment-for-me/

The Female ARAF Form (STEPS 1, 2, 3 and 4)

https://mhra-gov.ARAF

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KEY document completed by the SPECIALIST overseeing the Pregnancy Prevention Programme.
To support and document decisions and discussion with the patient or responsible person of the risks with valproate and the measures needed to minimise these risks.

Step 1: Specialist prescriber: Establish whether the patient is at risk of the reproductive harms of valproate

Step 2: Specialist prescriber and countersigning specialist: Document their prescribing decision.

A countersigning specialist is only required for women *newly starting* valproate and for existing female patients at *one annual review*. Subsequent annual reviews do not require the countersigning specialist unless the patient's circumstances have changed.

Step 3: Specialist prescriber: Explain the risks to the patient or responsible person.

Step 4: To be completed by the patient or responsible person

Confirms that, the patient (or responsible person), have discussed and acknowledge the risks of using valproate during pregnancy and the measures needed to reduce the risk.

Specialist team must give a copy of completed form to the patient or responsible person and store in their medical notes.
Share with patient's GP

ACTION:
General practice add SystmOne code Y362e 'Valproate Risk Acknowledgement Form completed'

The Female ARAF form STEP 1 https://mhra-gov.ARAF

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Annual Risk Acknowledgement Form for Female Patients
VALPROATE HAS RISKS IN PREGNANCY

Step 1 – Specialist prescriber: Establish whether the patient is at risk of the reproductive harms of valproate

The following issues should be considered when evaluating the risks associated with the use of valproate during pregnancy:

- Women of childbearing potential (from menarche to menopause) who are taking any medicine containing valproate, regardless of the indication, should fulfil all the conditions of **prevent** unless there are compelling reasons that there is no risk of pregnancy which should be documented below.
- If the potential for not becoming pregnant is permanent, the reason should be documented below and the conditions of **prevent DO NOT** need to be fulfilled.
- Female children who have not yet reached menarche (not started her periods) **DO NOT** need to fulfil the conditions of **prevent**, but they and their responsible person need to be aware of the risks for the future. You should provide a copy of the Patient Guide and remind the responsible person to contact their GP once the female child using valproate experiences menarche. Their GP will refer the patient back to the specialist prescriber.
- If the compelling reason(s) suggesting no risk of pregnancy may be subject to change, the risks should be discussed at subsequent annual reviews or sooner if their circumstances change.

If you consider there is a reason that indicates **prevent** does not apply, *tick* which reason applies and record here. If the reason is permanent, steps 2, 3 and 4 do not need to be completed.

To be completed by the specialist prescriber if they consider prevent - the valproate Pregnancy Prevention Programme (PPP) - is not needed
☐ The patient has not yet reached menarche at the time of this appointment. I have asked the patient and their family to inform their GP to refer the patient back to the specialist prescriber if this changes before their next annual review.
☐ The absence of pregnancy risk is considered to be permanent for the following reason (*insert reason*):
☐ There are other reasons that conditions of **prevent** are not applicable (*insert reason*):

Is there a *permanent* reason the reproductive risks of valproate DO NOT apply?

Female patients who have a permanent reason that they do not have the potential to get pregnant (e.g., post-menopausal patients or those after hysterectomy) do not need to complete this form beyond step 1. This form can be used to support documentation in the medical notes that prevent does not apply to this patient.

ACTION:

General practice add SystmOne code Y2f18 ‘Pregnancy Prevention Programme NOT needed’

BSW Primary Care Valproate Audit Findings – *Prescribing Quality Incentive Scheme 2022/23*

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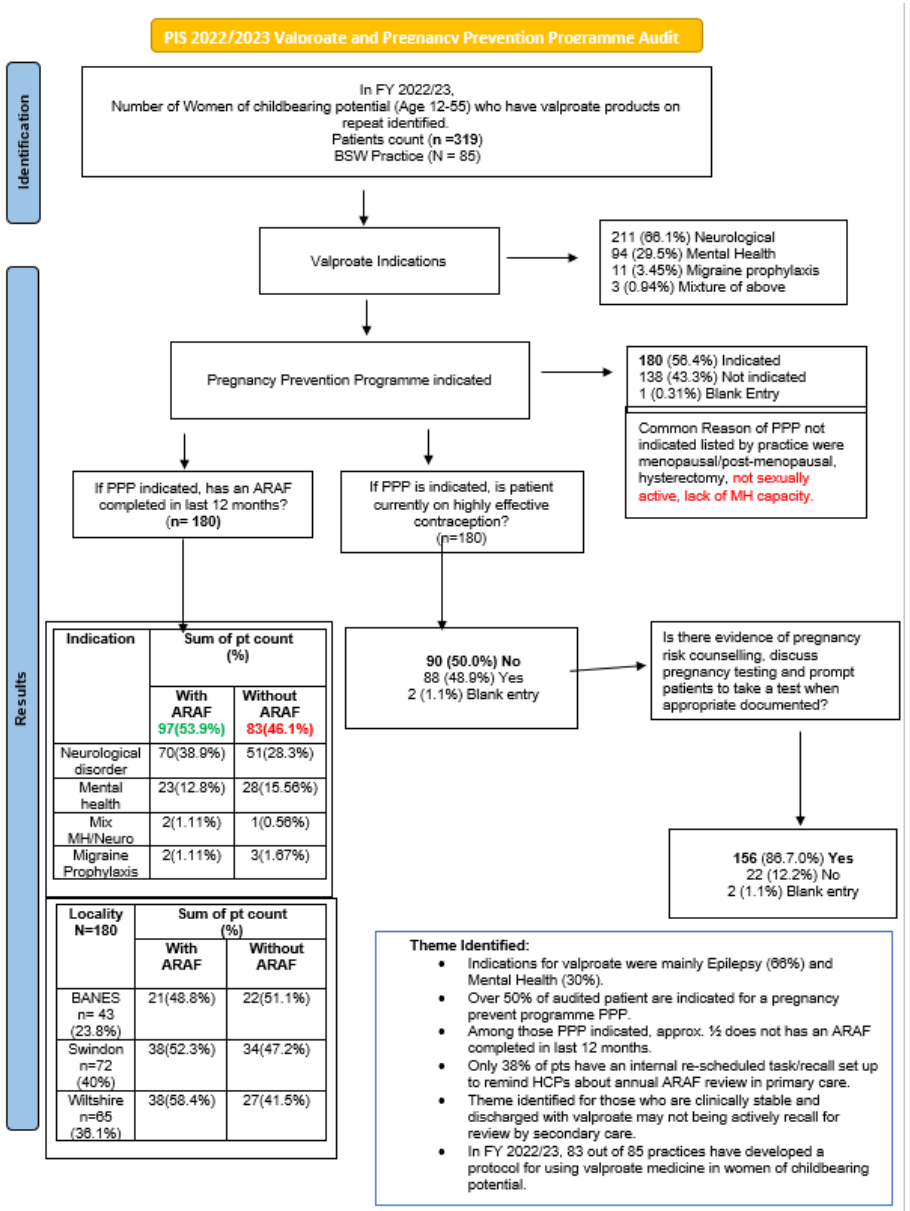

Primary Care Audit of GP Practice Records 2022/23

Women of childbearing potential (aged 12 – 55) prescribed valproate N = 319 within a total 85 GP Practice in BSW

Epilepsy 66%. Mental Health 30%. Migraine prophylaxis 3.45%

Approx. 180 patients indicated for a pregnancy prevent programme (PPP), of which 90 had no ARAF in last 12 months

Women of childbearing age (PPP indicated) who are prescribed valproate, approx. ½ are on highly effective contraception. Are we assured those 50% who are not receiving have made an informed decision to decline?

Approx. 1/3 patients have an internal re-scheduled task/recall set up to remind HCPs on valproate/ARAF review in primary care.

Theme observed: for those who are clinically stable and discharged with valproate may not be actively recalled for review by secondary care.

Contraception for women as part of the Pregnancy Prevention Programme

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Women of childbearing potential

Optimal choice is highly effective user independent form of contraception without interruption during the entire duration of treatment with valproate (**see guidance from Faculty of Sexual and Reproductive Health (FSRH)**).

Individual circumstances should be, in each case, evaluated when choosing the contraception method, involving the women in the discussion to guarantee engagement and optimal choice of contraception.

At initiation and at regular review at least every year, specialists should discuss the risks and document (ARAF) that they have been fully informed on the need to use highly effective contraception.

General practice should reinforce this message and **ensure ongoing use of highly effective contraception**.

Highly effective methods have typical-use failure rates of less than 1% and include the long-acting reversible contraceptives (LARC):

- copper intrauterine device (Cu-IUD),
- levonorgestrel intrauterine system (LNG-IUS),
- progestogen-only implant (IMP), and
- male and female sterilisation,

all of which have a failure rate of less than 1% with typical use.

If a user-independent form is not used, two complementary forms of contraception including a barrier method should be used and regular pregnancy testing considered. *The additional protective effect of using barrier method with oral contraception has not been quantified in the guidance* and is not considered to be as effective as a user-independent method.

Actions for GP Practices – Males

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Newly started males

- Likely to be few patients newly initiated. BSW formulary traffic light amber for males until detail of MHRA Phase 2 regulatory measures released

- **Specialist initiating will complete** Risk Acknowledgement Form for male patients starting valproate: 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 currently only to be completed at initiation of valproate (Phase 1 of new regulatory measures).

Existing Males

- **Currently no regulatory actions required by the MHRA. MHRA intend to release 'Phase 2' regulatory changes later in 2024 to cover existing males.** GOV Valproate Safety

- For clinicians who wish to act before the MHRA Phase 2 measures are announced the BSW Valproate Safety Working Group agreed that at the next scheduled/routine medication review, clinician can use the updated MHRA patient guide to facilitate a discussion with males about *potential* reproductive risks. Should be implemented safely via individual discussion with patient, to avoid causing alarm. NOT via Accurx text or letter. https://www.cas.mhra.gov.uk/CMO Valproate Safety Message

- Significant risk of harm if patient stops valproate abruptly without specialist input. Evidence of reproductive risks in males is still under review. Requires personalized delivery via a discussion.

- Consider January 2024 Drug Safety Update advice: 'As a precaution, male patients who are planning a family within the next year should speak to healthcare professional about their treatment'

- Specialists input will be required to provide advice on alternative treatment options and the benefits and risk associated with any changes.

Actions for GP Practices– Existing Females

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- Ensure females of childbearing potential prescribed valproate at your practice are identified (register/list). Are they enrolled in a Pregnancy Prevention Programme (PPP) with the relevant specialist team? Should they be?

- If there is a *permanent* reason the reproductive risks of valproate DO NOT apply add SystmOne CODE Y2f18 'Pregnancy Prevention Programme NOT needed' and reason e.g. hysterectomy, postmenopausal

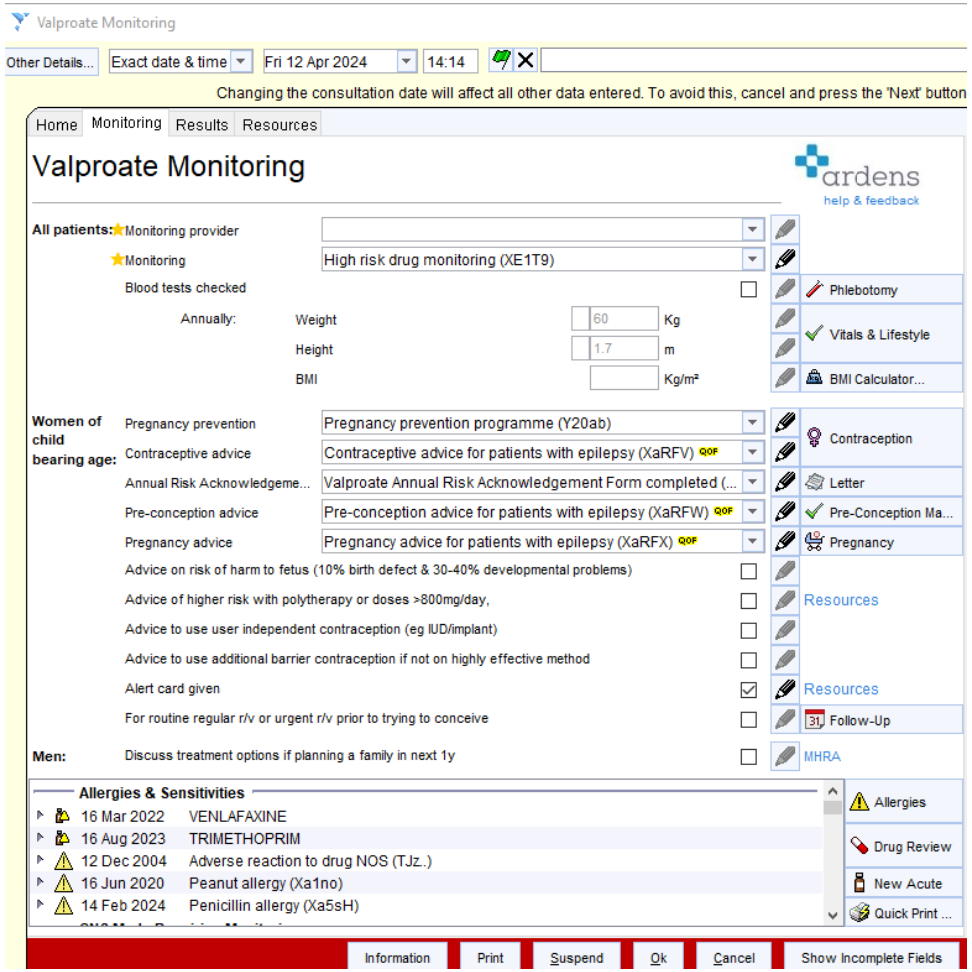
- Use the valproate monitoring template in Ardens to ensure accurate documentation/coding of PPP details To include but not limited to the following codes:
  - ***Pregnancy Prevention Programme started (Y2f16) OR***
  - ***Pregnancy Prevention Programme not needed (Y2f18)* OR**
  - ***Valproate Annual Risk Acknowledgement form completed (Y362e)***
  - ***Referral for completion of Valproate Annual Risk Acknowledge Form (Y38a6)***

- Prescribe or liaise with sexual health service to arrange appropriate *highly effective contraception* as per Faculty of Sexual Health and Reproductive Healthcare guidance

- At the point of issuing a repeat prescription, check there has been a review by a specialist in the last year and that an up-to-date Annual Risk Acknowledgement Form has been received by the practice.

- Ensure the patients has the patient information materials every time the patient attends their appointments or receive their prescriptions.

- Support women to seek advice from general practice or specialists as soon as possible if a pregnancy occurs or planning a pregnancy.



Actions for GP Practices – New Females

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- Likely to be very few patients newly initiated

- **Potential for not becoming pregnant is permanent,** the reasons for not enrolling on the Pregnancy Prevention Programme (PPP) must be documented in the primary care clinical system and record PPP not needed (**Y2f18**). *Hence annual recall of review ARAF is not applicable.*

- **Female children who have not yet reached menarche**, patient(s) and their responsible person need to be made aware the risk for the future. Remind to re-contact GP once female child using valproate experience menarche. *GP is responsible to facilitate the patient seek advice from specialist as soon as possible when the risk status changed.*

- **Women of childbearing potential (from menarche to menopause)** should be enrolled by the specialist onto the PPP unless compelling reason that there is no risk of pregnancy. Document Pregnancy Prevention Programme (**Y20ab**) AND Valproate Annual Risk Acknowledgement form completed (**Y362e**) in the primary care clinical system. Prescribe or liaise with sexual health service to arrange appropriate *highly effective contraception* as per Faculty of Sexual Health and Reproductive Healthcare guidance.

- BSW formulary traffic *Amber Shared Care* for females & Shared Care Agreement (SCA) is now available for female patients BSW-Valproate-SCA.

- Prescribe Valproate product as per SCA, add patient to your surgery valproate list to facilitate local safe Valproate prescribing procedure.

Other Actions for GP Practices

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- Agree/update your standard operating procedure (SOP) for safe valproate prescribing, monitoring and recall to include but not limited to:
    - Setting up and maintaining a surgery valproate list/register for the PPP.
    - Regular (monthly/quarterly) running valproate search to identify any new females prescribed valproate (either newly initiated or patients new to surgery) and check requirements are in place for existing females as appropriate e.g., ARAF, Highly effective contraception, annual review
    - Document the processes/steps implemented to facilitate recalls and monitoring. Support patient to attend the specialist appointment for review.
    - Searches for females prescribed valproate, documentation within patient notes and procedures for assurance around the PPP is covered in CQC assessments (currently females) https://bswtogether.org.uk/medicines/medications-and-cqc-assessment/
    - We can facilitate sharing examples of procedures on request *bswicb.prescribing@nhs.net*

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Thank you

Please get in touch if you're unsure, want to share examples of cases and highlight how the system is currently working, or if you'd like to be involved in ICS valproate safety improvement work *bswicb.prescribing@nhs.net*