Sodium Valproate – Actions to be taken to adhere to Pregnancy Prevention Program Update 2019

Background

Valproate is a medication used principally in the treatment of epilepsy and bipolar disorder. It is available in three formulations in the UK: sodium valproate, valproic acid and semisodium valproate. The most commonly dispensed valproate medicines in the UK are Epilim▼ and Depakote▼. Other brands available are Convulex▼, Episenta▼, Epival▼, Kentlim▼, Orlept▼, Syonell▼, and Valpal▼. Generic versions are also available.

Valproate is associated with a significant risk of birth defects and neuro-developmental disorders in children born to women who take valproate during pregnancy. In 2018 the MHRA issued guidance which stated valproate medicines **must no longer** be used in women or girls of childbearing potential unless a **Pregnancy Prevention Programme** (PPP) is in place.

Since the publication of the initial guidance, difficulties with the implementation have emerged and in March 2019 a cross-speciality consensus document was produced and the initial annual risk acknowledgement form (ARAF) was updated to address some of the challenges faced in practice.

The PPP is a system of ensuring all female patients who are at risk of pregnancy whilst taking valproate medicines:

1. Have been told and understand the risks of use of valproate in pregnancy and have signed a valproate Annual Risk Acknowledgement Form (AFAF) See Appendix 1 for a copy of the ARAF (2019 version).
2. Are on highly effective contraception if necessary – see Appendix 2.
3. Are reviewed by their specialist at least every year.

It is important to note that the use of valproate in pregnancy **is contraindicated for bipolar disorder** and must only be considered for epilepsy if there is no suitable alternative treatment.

Primary Care Prescribers' Responsibilities*

Prescribers involved in the care of women and girls of childbearing potential using valproate medicines for any indication must:

- Read the Guide for Healthcare Professionals.
- Identify all female patients of childbearing potential from the ages of 10 to 55 years on valproate medicines (excluding those who are permanently at no risk of pregnancy e.g. have had a hysterectomy or who have proven menopause) and recall for a review. **See appendix 3 for a sample patient information letter.**
- Refer patients to the Consultant Neurologist/Psychiatrist according to the pathway if they have not been reviewed in the last 6 months and/or do not have a completed ARAF**. See appendix 4 for sample referral letter.**
- Arrange for highly effective contraception (HEC) if not already using. See appendix 2.
- Ensure the patient understands the need to comply with contraception throughout treatment and undergo pregnancy testing when required e.g. if there is any reason to suggest lack of compliance or effectiveness of contraception.

- Ensure all women and girls (and their parent, caregiver, or responsible person, if necessary) are fully informed of the risks to the unborn child of using valproate during pregnancy and provide the Patient Guide.
- Inform patient to contact you immediately if she suspects there has been a problem with her contraception or she may be pregnant.
- Ensure that all women of child bearing potential taking valproate medicines have an annual review with the Consultant Neurologist/Psychiatrist and patients are reminded of this.
- Ensure a new ARAF is completed annually, that the patient has a copy of the completed ARAF (see Appendix 1) signed by the Neurologist / Psychiatrist and that a copy is saved on the patients' record in the GP practice.
- **Please note that these responsibilities are reflected on template searches on GP clinical systems.**

Specialist Responsibilities*

Specialist prescribers involved in the care of women and girls of childbearing potential using valproate medicines for any indication must:

- Book in review appointments at least annually with female patients under the PPP and re-evaluate treatment as necessary.
- Implement the PPP for patients continuing valproate medicines after review.
- At initiation and at a review at least every year, specialists should discuss with the patient the risks of valproate in pregnancy and the need for her to be on valproate. Complete and sign the Annual Risk Acknowledgement Form (ARAF) with the patient (or their parent/caregiver/responsible person). This is to record that they have discussed and understood the risks and have been fully informed on the need to use highly effective contraception, without interruption, during the entire duration of treatment with valproate. This may be necessary for women not currently sexually active if pregnancy is possible.
- Ensure a copy of the completed ARAF is given to the patient /caregiver/responsible person.
- Forward a copy of the ARAF to the patient's GP along with their discharge summary or clinic letter.

Page 3 outlines a proposed approach to reviewing women of childbearing potential on valproate in primary care and managing referrals for specialist review.

- Please note that the referral pathway is for guidance and patients should be assessed individually taking all relevant clinical issues into consideration.
- The referral pathway relies on the GP making an estimation of pregnancy as low, moderate or high. Examples are given on the pathway to aid risk categorisation, however GPs should note that this is not exhaustive and risk needs to be considered for each individual.

*Ensure processes are in place for providing relevant information to patients where English is not their first language, patients with intellectual disability, and girls under the age of 16 years.

A leaflet specifically for girls and young women can be found in the link below:
www.medicinesforchildren.org.uk/sodium-valproate-and-pregnancy

More advice on implementation of the PPP in children under 16 and in people of all ages with intellectual disability is available in the consensus document.

Valproate review– a possible practical approach

Is the patient of child-bearing age (10-55)?

No → Box A:
- Patient to be sent GP template letter advising on valproate risk together with MHRA Valproate Patient Guide.
- Document patient assessment with rationale and record that contact has been made on patient records.
- Ensure all patients are reviewed regularly by the relevant specialist, including all girls aged 10-15
- Do not stop prescribing valproate except upon advice from a specialist.

Yes ↓

Is she able to have children?
(exclude patients who have had hysterectomy or have proven menopause)?

No → Box A

Yes ↓

Is the patient already pregnant/planning a pregnancy?

Yes → Refer urgently to neurologist or psychiatrist
For urgent referrals (within days): GP to telephone the neurology/psychiatry secretary and ask for urgent review.

No ↓

Is the patient already on the Prevent programme?
(i.e.is she on highly effective contraception and has annual risk assessment form completed)

Yes → Manage as in Box A.
Ensure seen annually by specialist.

No ↓

Review as per recommendations in Table 1.

Table 1: Recommendations for review of women of childbearing potential on Valproate (In all cases, ensure recommendations in Box A are met).

Last review date	**Recently (within the last 6 months)**			**Coming up in next 6 months**		**Not currently under review by specialist**
Risk of pregnancy as per categories below	Low	Moderate	High	low/moderate	High	Low/moderate/high risk of pregnancy
Actions to be taken	Letter to consultant asking to include ARAF in review at next planned appointment	Letter to consultant asking to bring next appointment forward and to include ARAF		Letter to consultant asking for ARAF to be completed at next appointment. Consider asking for appointment to be brought forward if risk is high		Call patient in for GP appointment (urgency dependent on risk). At appointment discuss HEC and re-referral to specialist

Example risk categorisation (not exhaustive and to be considered individually for patient)

Low risk – On HEC but ARAF not completed; monogamous partner has had vasectomy; not sexually active; not sexually active with male partner; patient with learning disability living in own home under supervision – carers confirm risk of pregnancy low

Moderate risk – Menopausal/upper end of age group and is actively avoiding pregnancy; on single, user dependent form of contraception (including Depo-provera); LD user in care setting with high supervision – carers confirm risk of pregnancy not high

High risk – Chaotic lifestyle; previous unplanned pregnancy; previous pregnancy on valproate; LD patient lives independently or in care setting with low supervision.

HEC – Highly effective contraception; ARAF – MHRA valproate Annual Risk Acknowledgement form. MHRA Guidance.

Appendix 1

Valproate in female patients - Annual Risk Acknowledgment Form is available in the link below. (Revised November 2019)

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/860762/Risk-acknowledgment.pdf

Appendix 2 - **Contraception and the Prevent Programme**

As with all teratogenic medicines, pregnancy should be excluded before initiation on valproate medicines with a negative plasma pregnancy test, confirmed by a healthcare professional.

The MHRA guidance recommends that women and girls of childbearing potential taking valproate must use highly effective contraception (see guidance from Faculty of Sexual and Reproductive Health [FSRH]).

Effective contraception is essential while taking valproate. Neither condoms nor oral contraceptives alone are sufficient.

Methods of contraception considered 'highly effective' in this context include male and female sterilisation (with male sterilisation, the possibility of a new partner needs to be kept in mind) and the long-acting reversible contraceptives (LARC):

- Copper intrauterine device (Cu-IUD)
- Levonorgestrel intrauterine system (LNG-IUS)
- Progestogen-only implant (IMP)

All of which have a failure rate of less than 1% with typical use (see guidance from FSRH for more information about user-independent methods and failure rates).

Appendix 3

PRACTICE SAMPLE LETTER

Dear Patient

Re: Valproate and Pregnancy

This letter has been sent to you by your doctor as you have been identified as taking a medicine which contains valproate and because you are at a child bearing age.

- Valproate is an effective medicine used to treat epilepsy and bipolar disorder.
- Valproate can seriously harm an unborn child when taken during pregnancy and should be not taken by women and girls unless nothing else works.
- Women who have to take valproate should always use reliable contraception to avoid having an unplanned pregnancy.
- If you are thinking about having a baby, do not stop using contraception until you have discussed it with your doctor.
- Tell your doctor at once if you think you may be pregnant or know you are pregnant.

Never stop taking valproate unless your doctor tells you to as your condition may become worse.

Patient Guide has been enclosed together with this letter to provide you with more information.

I would be grateful if you could book an appointment via the reception to see me at your earliest convenience so we can talk through your individual circumstances.

I look forward to seeing you soon

Yours sincerely

Appendix 4

GP PRACTICE DETAILS

Address 1
Address 2
Doctors' Details

PRIVATE AND CONFIDENTIAL
Neurology/Psychiatry Consultant team
Medway Hospital
Windmill Road
Gillingham
ME7 5NY

Date as post mark

Dear Neurology/Psychiatry Team

Re <<Patient details>> Valproate use in Women and girls of childbearing age

I have reviewed this patient in accordance with the MHRA guidance on women of child bearing age taking valproate medicines.

1. <<patient name>> was last seen by your team <date last appointment> and is due to be seen again on <date of predicted appointment> **OR**
2. <<patient name>> was last seen by your team <date last appointment> and currently has no planned appointment> **OR**
3. <<patient name>> has not been seen by your team and under MHRA guidance needs to be under Neurology/Psychiatry services.

Patient takes <insert patient drug details> [name and form of drugs/ dose/ Frequency] [Indication].

She has been notified of the risk of her [Name/ form of Drugs……..] and pregnancy by <form of communication with patient> and has been given a copy of the Patient Guide with all relevant information.

- I consider this patient to be low risk for pregnancy because <*Insert details e.g. not sexually active with male partner; Learning Disability (LD) patient living in own home under supervision – carers confirm risk of pregnancy is low*>
- I am therefore happy to continue prescribing valproate at this time, however, I would be grateful if ongoing use is reviewed and the Annual Risk Acknowledgement Form is completed as required by the MHRA at her next appointment.

  OR

❖ I consider this patient to be moderate risk for pregnancy because <Insert details e.g. Menopausal/upper end of age group and is actively avoiding pregnancy; on single, user dependent form of contraception (including Depo-provera); patient with learning disability in a care setting with high supervision – carers confirm risk of pregnancy not high>

❖ I am happy at this time to continue prescribing valproate, however I would be grateful if you could arrange for her to be seen <earlier than planned/at your earliest convenience> so ongoing use is reviewed and the Annual Risk Acknowledgement Form can be completed as required by the MHRA. Please refer the patient to me for a discussion around highly effective contraception should this be necessary.

OR

➢ I consider this patient to be high risk for pregnancy because as described <Insert reason e.g. *previous unplanned pregnancy; previous pregnancy on valproate; LD patient lives independently or in care setting with low*>

➢ I will continue to prescribe valproate however I would be grateful if you could arrange for her to be given an appointment to see you as soon as possible so ongoing use is reviewed and the Annual Risk Acknowledgement Form can be completed as required by the MHRA. Please refer the patient to me for a discussion around highly effective contraception should this be necessary.

We will require a copy of the completed and signed Annual Risk Acknowledgement Form to be sent to us for our records.

Kind Regards
Dr <<Name>> General Practitioner
CC <<patient name>>

Further information

1. Further information can be accessed via Pregnancy Prevention Programme materials online. Available at: https://www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-pregnancy-prevention-programme-materials-online

2. The link below provides printable versions of the communication materials:
    a. Patient Card – to be given by pharmacists to all female patients who are dispensed valproate medicines to inform them of the risks

    b. Patient Guide – to be provided to girls (of any age) and women of childbearing potential (or their parent/caregiver/responsible person) taking any medicine containing valproate

    c. Guide for Healthcare Professionals – for all prescribers, pharmacists, and other healthcare providers involved in the care of women and girls of childbearing potential using valproate medicines

    d. Annual Risk Acknowledgement Form for the specialist and patient (or their parent/caregiver/responsible person) to sign at initiation and at treatment reviews at least every year. The patient should receive a copy of the form; one copy should be filed in the specialist notes, and one copy sent to the patient's GP

3. Hard copies of these materials can be ordered by contacting the Sanofi Medical Information Department on 0845 372 7101, or via e-mail UK-Medicalinformation@sanofi.com

4. More detailed information about valproate can be obtained by consulting the most recent Summary of Product Characteristics (SPC), available online through the eMC website (www.medicines.org.uk)