Procedure for management of female outpatients, already prescribed valproate

Prescribing valproate to a woman of childbearing potential without the pregnancy prevention programme (PPP) conditions being fulfilled is contraindicated and represents an unlicensed use of the drug.[1,4]

This procedure is a risk minimisation measure aimed at minimising pregnancy exposure during treatment with valproate. Before prescribing valproate to female patients, read the MHRA's "Guide for Healthcare Professionals - Information on the risks of Valproate use in girls (of any age) and women of childbearing potential". [1]

KEY POINTS TO BE COVERED AT SPECIALIST REVIEW:

- **INVITE:** Ensure that you invite all female patients (pre-menarchal or of childbearing potential, including those with compelling reasons not to be on a PPP) for an annual review. Continue treatment with valproate only if other treatments are ineffective or not tolerated and pregnancy is excluded by means of a negative pregnancy test.

- **DISCUSS:** Discuss the need for her to be on the pregnancy prevention programme if she is to continue taking valproate. (If she is not on a PPP, just complete pages 1 and 2 of the form. But if possible, page 3 & 4 should be completed so that the patient is aware of the risks if their situation were to change in the future). Patients prescribed continuing valproate treatment should also have an annual review of the risk-benefit balance, and this should be documented in their record. This should include assessment of therapeutic benefit, adverse effects and medication adherence.

- **EDUCATE:** Ensure she understands the risks to the unborn child of using valproate during pregnancy and provide the Patient Guide.

- **EDUCATE:** Ensure she understands the need to comply with highly effective 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.

- **DOCUMENT:** Complete and sign the Annual Risk Acknowledgment Form (ARAF) (at initiation and every annual visit); give a copy to her and send one to her GP.

- **REFER:** Refer for contraception services as needed.

Refer to the Healthcare professionals guide if patient is planning to become pregnant, or is now pregnant.

For new patients, only start treatment with valproate if other treatments are ineffective or not tolerated and pregnancy is excluded by means of a negative pregnancy test. Assess potential for pregnancy and if necessary discuss the need for her to be on the pregnancy prevention programme if she is to take valproate. Complete their initial annual review.

The algorithm below covers these points, and can be used to support initial and annual reviews, and valproate reviews done at any other time.

If the patient is post-menarchal, but not of childbearing potential, they are exempt from the requirement to complete the ARAF each year. They should be reviewed as per patients not on valproate, but checks should be made to check their last ARAF is up to date.

Prescribing valproate to a woman of childbearing potential without the pregnancy prevention programme (PPP) conditions being fulfilled is contraindicated and represents an unlicensed use of the drug.[1,4]

1. Establish whether the risk of pregnancy is currently excluded

Is patient pre-menarchal?

Yes → The patient does not need to be on a pregnancy prevention programme, but this review should be completed. Go to step 3.

No → Is patient post-menopausal, or **permanently** not of childbearing potential, e.g. hysterectomy, sterilisation.

Yes → The patient does not need to be on a pregnancy prevention programme. Review their existing annual form. Go to step 6.

No → Is patient of childbearing potential but there is a compelling reason to indicate that there is no risk of pregnancy, and is therefore not on a pregnancy prevention programme?

No → Patient should be on a pregnancy prevention programme. Continue to step 2.

Yes → The patient does not need to be on a pregnancy prevention programme, but this review should be completed. Go to step 3.

2. A review of the patient's Pregnancy Prevention Programme (PPP) should be undertaken.

Prescriber to commence data gathering

- Why is she using valproate (is it for bipolar / epilepsy / other)?
- Ask if she is aware of the need for highly effective contraception, and the need to be on a Pregnancy Prevention Programme while taking valproate.
- Is she on a PPP?
- What type of contraception is she using for the PPP?
- Has this contraception been used uninterrupted, with full compliance and full effectiveness?
- Has she recently had unprotected sex that might have resulted in pregnancy?
- Inform her of the known risks of valproate in pregnancy, and ensure that she understands she must not get pregnant whilst taking valproate.
- Ask when her last annual valproate review was with her specialist (psychiatrist/ neurologist/ paediatrician).
- Look for her Annual Risk Valproate form in electronic patient record (print if found).

Now continue to step 3.

3. Establish reason for using valproate		
Is valproate being used for a licensed indication (i.e. bipolar or epilepsy) or unlicensed-but-approved* indication (i.e. valproate in bipolar)?	No →	Confirm the reason for valproate use with that prescriber, e.g. neurologist. The responsibility for review lies with that prescriber. Continue to step 5.

Yes

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Licensed/ unlicensed-but-approved indications are:*	*"Off-label" uses might include compulsive & aggressive behaviour, depression, neuropathic pain, dementia, migraine, as mood stabiliser, or to prevent clozapine-induced seizures..*
*Treatment of epilepsy (with **valproate**); Treatment (with **valproate*** or **'Depakote'**) of manic episode in bipolar disorder when lithium is contraindicated or not tolerated / continuation of treatment after manic episode in patients who have responded to valproate* or 'Depakote' for acute mania.*	

4. Review the treatment	
VALPROATE USED FOR BIPOLAR	VALPROATE USED FOR EPILEPSY
Only continue if valproate represents the best treatment option for bipolar after assessing the risks/benefits, and/or other treatments are ineffective or not tolerated.	*Do not stop treatment without discussion with specialist who regularly manages her epilepsy. The responsibility for annual review lies with the epilepsy specialist.*
Is valproate treatment to continue?	

Yes No ↘

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The conditions of the pregnancy prevention programme (PPP) continue to apply until the switch from valproate is complete. Refer to guidelines[1] on "Switching or discontinuing valproate".

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5. Establish current risk of pregnancy			
Review information gathered so far, about possibility of pregnancy: ○ *Establish whether there is any possibility that she has recently had unprotected sex;* ○ *Establish whether there is possible non-compliance or non-effectiveness of contraception, e.g. use was interrupted;*			
Where necessary, refer her for highly effective contraception.			
Pregnancy tests may not detect an early pregnancy that has occurred after unprotected sex in the preceding 3 weeks. Therefore, women should have a repeat pregnancy test 3 weeks after starting a new contraceptive method if there was any risk of pregnancy at the start of the contraceptive method, even if the first test was negative. [1]			
Unplanned pregnancy: Refer to guidelines [1] *and SPC* [4]*.*			
Could patient be pregnant?			
No	Yes, could be pregnant	No	Yes, could be pregnant

VALPROATE USED FOR BIPOLAR		VALPROATE USED FOR EPILEPSY	
Continue valproate treatment for bipolar.	Pause valproate treatment for bipolar. If possible risk of pregnancy, or is pregnant, valproate should be switched to another treatment, and the patient's treatment reviewed immediately. If clinically appropriate, the drug can be restarted provided that a negative serum hCG pregnancy test has been obtained a minimum of 14 days after the last possible day on which she could have had unprotected sex.	Continue valproate treatment for epilepsy as directed by specialist.	If possible risk of pregnancy, or is pregnant, valproate should **not** be stopped for epilepsy. Her neurology team must be consulted. This consultation should be considered extremely urgent (within days) and should occur at the earliest possible opportunity after she is seen. The consultation should involve a thorough discussion about the risks posed by either continuing the valproate or stopping it.
Now continue to step 6.			

6. Review "Annual Risk Acknowledgement Form, Valproate has risks in pregnancy"
NOTE: If the valproate is prescribed by another specialist other than your specialty, e.g. neurologist, the responsibility for valproate prescribing and annual review lies with that specialist. However it is best practice to confirm with that specialist that their annual review has taken place, as failure to be reviewed will put the patient at risk. For example, in psychiatry, if the patient's valproate is for a non-psychiatric condition, write to the GP stating that the patient has been seen, but that the responsibility for valproate review lies with another specialist, and therefore has not been completed during this review.
The following steps apply to the patient taking valproate for a condition for which you are the specialist.
If risk of pregnancy is currently excluded, but might change (e.g. pre- menarchal or she has a compelling reason not to be on a PPP), the form must still be completed. (Page 1 and 2 of form only, page 3 & 4 can be left blank. But if possible, page 3 & 4 should be completed so that the patient is aware of the risks if their situation were to change in the future.)
If risk of pregnancy is permanently excluded, check that the most recent annual form accurately reflects this. Continue below.
*If there is **any** risk of pregnancy they must be on a PPP. Complete all 4 pages of form.*

Can her current "Annual Risk Acknowledgement Form, Valproate has risks in pregnancy" be found in the medical record?

Yes ↓

No ↓

Review content of current "Annual Risk Acknowledgement Form, Valproate has risks in pregnancy"

Is it up to date (within last 12 months), and completely and accurately reflects her current medical history and risks, and confirms that she is fulfilling all conditions of the PPP (where in place)?

Yes ↓

No → Complete new form ↓

Continue to prescribe valproate for your specialty, if appropriate, and if all conditions of PPP are fulfilled (where in place).

Write to GP confirming that the patient's annual valproate review continues to be the responsibility of your speciality, and it is currently in date, and a repeat valproate annual review will be completed before the expiry date.

Email EPUT pharmacy, informing them that a review has been completed for this patient.

Pharmacy: on receipt of email from specialist, update the patient's PMR on Ascribe.

END OF PROCEDURE

Continue to prescribe valproate for your specialty, if appropriate, and if all conditions of PPP are fulfilled (where in place).

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Specialist: provide patient a copy of the Annual Risk Acknowledgement Form.

Medical secretary: Scan the new valproate form to medical record (see Appendix 4). For CHS patients, contact your pharmacy team for advice.

Medical secretary: Write to GP, including the new form (original paper form or scan), confirming that the patient's annual valproate review continues to be the responsibility of the EPUT specialist, and that the valproate annual review was just completed, and will be repeated in 12 months. Scan copy to medical record (see Appendix 4). For CHS patients, contact your pharmacy team for advice.

Email EPUT pharmacy, informing them that a valproate review has been completed for this patient.

Pharmacy: on receipt of email from specialist, update the patient's PMR on Ascribe.

END OF PROCEDURE