Kent and Medway
NHS and Social Care Partnership Trust

Protocol for using valproate in women of childbearing potential and for males younger than 55 years

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DOCUMENT TRACKING SHEET

Protocol for using valproate in women of childbearing potential

Version	Status	Date	Issued to/approved by	Comments
1	Ratified: 3rd of October 2017	October 2017	Author: Jagdip Bahia	
2	Ratified: 5th December 2017	November 2017	Author: Jagdip Bahia	• New guidance published by the European Medicine Agency public hearing on valporate prescribing in pregnancy on 27th of September 2016 which recommends: **" Regular (at least annual) reviews for all women receiving long-term valproate were supported, to ensure that their understanding of the risks and benefits was updated appropriately as their life plans change"** • Prescriber checklist updated from 6 monthly reviews to annual reviews
3	Ratified: 7th of August 2018	August 2018	Author: Jagdip Bahia	• In May 2018 the MHRA strengthened its regulatory position on valproate medicines. Valproate must no longer be used in any woman or girl able to have children unless she has a pregnancy prevention programme in place. This is designed to make sure patients are fully aware of the risks and the need to avoid becoming pregnant. • Exclude pregnancy in women of childbearing potential (by serum pregnancy test) before the first prescription is issued. • Arrange for highly effective contraception for women of childbearing potential before the first prescription is issued. • Two checklists implemented in the guidance for prescribers. One for new female patients prescribed valproate and the other is for existing patients. • For patients who are assessed to lack capacity to consent to treatment then prescribing of valproate should be avoided. If a decision is made to initiate valproate then it should only be done on a KMPT inpatient ward after getting a second opinion from another Consultant. A best interest meeting needs to be arranged for all patients without the capacity to make an informed decision.

				• New Section 3 Action for pharmacists • Annual Risk Acknowledgment Form updated as per MHRA guidance
4		Dec 2018	Author: Jagdip Bahia	• The Royal College of Psychiatrists have published guidance for prescribers on the withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness.
5	TBC	May 2019	Author: Angie Lehman	• Updated guide for completing the Annual Risk Acknowledgement Form
6	**Final**	Ratified 2nd June 2020	Author: Angie Lehman **Approved by:** Drugs and Therapeutics Committee	• Updated contact details and email addresses • Updated flow chart
6.1			Author: Lola Ogungbangbe **Approved by:** Drugs and Therapeutics Committee	• Section 1 updated with NICE and RCOG guidance on diagnosing menopause in women • Updated to reflect absolute contraindication in pregnancy.
7	**Final**	Ratified 6th of April 2021	Author: Lola Ogungbangbe **Approved by:** Drugs and Therapeutics Committee	• Highlighting the message Valproate should **NEVER** be prescribed to pregnant women for the indication of bipolar disorder. • Detailed information on confirming absence of risk of pregnancy
8	**Final**	Ratified 7th of June 2022	Author: Jagdip Bahia **Approved by:** Drugs and Therapeutics Committee	• Initiation must be done by a Consultant Psychiatrist, but other responsibilities may be carried out by other healthcare professionals as part of a Consultant led team; Non-Medical Prescribers and Advanced Clinical Practitioners.
9	**Draft**		Author: Jagdip Bahia Approved by:	• Updated following National Patient Safety Alert (NatPSA/2023/013/MHRA)

SUMMARY OF CHANGES

Date	Author	Page	Changes (brief summary)
March 2021	Lola Ogungbangbe	1	• Valproate should not be prescribed to women or girls of child bearing potential unless other treatments are ineffective or not tolerated. • Valproate should **NEVER** be prescribed to pregnant women for the indication of bipolar disorder.
March 2021	Lola Ogungbangbe	5	• New section 2.1.5 confirming absence of risk of pregnancy
July 2021	Jagdip Bahia	2	• Initiation must be done by a Consultant Psychiatrist, but other responsibilities may be carried out by other healthcare professionals as part of a Consultant led team; Non-Medical Prescribers and Advanced Clinical Practitioners in such teams should be considered as specialists for this situation, allowing them to complete annual reviews for continuation of treatment.
January 2024	Jagdip Bahia		• Update to title to reflect addition of guidance affecting males • Update background following NatPSA Nov 23

			• Update 2.1 Section A – need for two independent specialists • Addition of 2.1 Section C and D for review of males prescribed Valproate • Updated 2.2 – Who can be the second specialist signatory

CONTENTS

1 BACKGROUND

- Valproate is a medication used in the treatment of epilepsy and bipolar disorder.

- Valproate is available in three formulations in the UK: sodium valproate, valproic acid and semisodium valproate.

- *In utero* exposure to valproate is associated with serious adverse effects for the developing child, including:

    - Congenital malformations:
      These are seen in approximately 10% of cases and include: neural tube defects (spina bifida, anencephaly), facial dysmorphia and cardiac malformations.
    - Developmental disorders:
      These are seen in approximately 30-40% of cases and can include an increased risk of autistic spectrum disorder (approximately three-fold increase in risk), childhood autism (approximately five-fold increase in risk) and delays in early development. There is evidence that children exposed to valproate *in utero* will go on to have a lower IQ than children exposed to other antiepileptic drugs.

- As a result of this risk, the Medicines and Healthcare products Regulatory Agency (MHRA) published a Drug Safety Update (Valproate and risk of abnormal pregnancy outcomes: new communication materials) in February 2018 and the valproate Pregnancy Prevention Programme (prevent) in May 2018, stating that:

    - Valproate should not be prescribed to women or girls of child bearing potential unless other treatments are ineffective or not tolerated.

    - Valproate should **NEVER** be prescribed to pregnant women for the indication of bipolar disorder.

    - Valproate may be initiated in women of childbearing potential only if the conditions of the Pregnancy Prevention Programme are fulfilled. This is outlined in the prescriber checklist (see Section 2.1).

    - Valproate can only be started and supervised by a Consultant experienced in managing epilepsy or bipolar disorder.

    - Female patients and their carers should be counselled about the risk of taking valproate during pregnancy.

    - For females planning to become pregnant, all efforts should be made to switch to an appropriate alternative treatment prior to conception.

- The Drug Safety Update also stipulated communication materials which the MHRA have asked healthcare professionals to use when valproate is prescribed for females of childbearing potential. These communication materials have been incorporated into the protocol for valproate use set out in this document.

- A National Patient Safety Alert was issued in November 2023 which included concerns surrounding the known possible risk of impaired fertility in males, thought to be reversible upon dose reduction or discontinuation and has been in the product information since 2011. The following MHRA report, Valproate: review of safety data and expert advice on management of risks provides further detail on these concerns which have led to

additional regulatory measures with the key one being that valproate must not be started in male patients younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or unless there are compelling reasons that the reproductive risks do not apply.

2 PRESCRIBING VALPROATE

2.1 Prescriber checklist

Section A: New female patients

- Two specialists need to independently consider and document in the patients RiO progress notes that there is no other effective or tolerated treatment for patients aged under 55 years before valproate is initiated.

- Ensure other treatments are ineffective or not tolerated before considering prescribing valproate and discuss the risks with the patient.

- Exclude pregnancy in women of childbearing potential (by serum pregnancy test) before the first prescription is issued (further details in Section 2.1.5).

- Arrange for highly effective contraception for women of childbearing potential before the first prescription is issued.

- Highly effective contraception includes methods such as the long acting reversible contraceptives (LARC), copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS), progestogen-only implant (IMP) and female sterilisation, all of which have a failure rate of less than 1% with typical use.

- User dependent methods such as the condom, cap, diaphragm, combined oral contraceptive pill (COC) or progestogen-only contraceptive pill (POP) and fertility awareness-based methods are not considered highly effective since the typical use incorporates user failure risks.

- Ensure 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. Refer for contraception services as needed.

- Complete the Annual Risk Acknowledgment Form with patient (Appendix 1). This will need to be **signed by the second specialist** if the patient is to continue with valproate. Give the patient a copy, send a copy to the GP, upload to the patient's electronic RiO notes and send a copy to the KMPT Medicines Safety Officer (kmpt.mso@nhs.net). This risk form combines the MHRA's checklist requirements with KMPT specific requirements.

- Provide a copy of the Patient Guide to the patient.

- Ensure that all women of child bearing potential have an annual review. This responsibility should be carried out by the Consultant Psychiatrist or other healthcare professionals as part of a Consultant led team including Non-Medical Prescribers (NMPs) or Advanced Clinical practitioners (ACPs) as long as it's in their scope of practice. In such teams NMPs and ACPs should be considered as specialists for this situation, allowing them to complete annual reviews for continuation of treatment. The Consultant should be available to

support the NMP and ACP if any problems arise in completing the Annual Risk Acknowledgment Form.

Section B: Existing female patients on valproate

- Identify all women of childbearing potential on valproate and arrange for highly effective contraception to be initiated for those not already on it or using contraception not deemed highly effective (as detailed in Section A: New female patients).

- Ensure patient understands the risks of using valproate during pregnancy to the unborn child and provide the Patient Guide (see link in Section A: New female patients).

- Ensure 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 to or effectiveness of contraception.

- Tell patient to contact you immediately if she suspects there has been a problem with her contraception or she may be pregnant.

- Ensure patient has the Annual Risk Acknowledgment Form (Appendix 2) signed by the Consultant Psychiatrist, a copy sent to the GP, uploaded to the patient's electronic RiO notes and sent to the KMPT Medicines Safety Officer (kmpt.mso@nhs.net). If the patient's situation has changed since the last review then the Annual Risk Acknowledgment Form will need to be signed by the second specialist.

- Remind the patient that they will need to see their Responsible Consultant at least every year for a review for as long as they are on valproate.

- The Royal College of Psychiatrists have provided guidance for prescribers on the withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness. The guidance summarises evidence for alternatives to valproate and provides advice on how women who are currently undergoing treatment with valproate medicines can be switched to alternative treatment. Available at: https://www.rcpsych.ac.uk/docs/default-source/improving-care/better-mh-policy/position-statements/ps04_18.pdf?sfvrsn=799e58b4_2

Risk assessment

- Prescribers must read the Guide for Healthcare Professionals involved in the care of women and girls of childbearing potential using valproate medicines.

- Prescribers must always carefully balance the benefits of valproate treatment against the risks. Valproate should only be used when other treatment options have been ineffective or have not been tolerated.

Capacity assessment

- Prescribers must ensure that the patient's capacity to consent to treatment has been assessed and has been documented in their medical notes.
- If patients are found to lack the capacity to consent to treatment, prescribers should follow the guidance in section 2.3 of this document.

Information provision

- It is the responsibility of the prescriber to ensure that the patient is provided with all necessary information about the risk posed by valproate use during pregnancy.

- Prescribers must ensure that the patient has been provided with a copy of the Patient Guide: What women and girls need to know about valproate. (See Section A:New Female Patients above for link)

- Prescribers must ensure that the patient has been informed about the need for effective contraception and has been given information about contraception methods.
- Prescribers must ensure that the patient has been informed to promptly contact them if she is planning a pregnancy or becomes pregnant.

Obtaining consent

- Prescribers should ask the patient to complete Step 4 of the Annual Risk Acknowledgment Form so that the patient understands the risks of taking valproate in pregnancy.

- The completed consent form must be uploaded to the patient's electronic RiO notes within clinical documentation and saved with the filename 'PREVENT dd/mm/yy'.

Risk reduction strategies

  - **Pregnancy testing:**

    - Prescribers must ensure that a patient has had a negative pregnancy test prior to starting valproate.

    - The aim of pregnancy testing is to provide as much certainty as possible that the service user is not pregnant, *before* prescribing valproate.

    - Pregnancy testing relies on detection of human chorionic gonadotropin (hCG), which is released after a fertilised egg has implanted into the uterus wall.

    - Implantation normally occurs 6 to 12 days after ovulation. As hCG will not be released until after implantation, there is a delay between the time of fertilisation of an egg and the time at which a pregnancy is detectable.

    - In the early stages after implantation, an hCG serum test more sensitively detects pregnancy than an hCG urine dip test.

    - Therefore, if there is any possibility that the patient has recently been sexually active, valproate should not be prescribed until:

      - 14 days have elapsed since the last possible day on which the patient could have had unprotected sex (for example, this could be 14 days from the point of admission, or 14 days from the last day on which the patient was given unescorted leave from the ward), **AND** a negative hCG serum test has been obtained

    - If there is the possibility that any patients who have been admitted who were already prescribed valproate in the community have recently had unprotected sex, the

valproate should be stopped. If clinically appropriate, it can be restarted provided that a negative serum hCG test has been obtained a minimum of 14 days after the last possible day on which the patient could have had unprotected sex.

- **Advising about contraception:**

  - Prescribers must advise patients on the need for effective contraception. These includes methods such as the long acting reversible contraceptives (LARC), copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS), progestogen-only implant (IMP) and female sterilisation, all of which have a failure rate of less than 1% with typical use. The progesterone-only injectable is reported to have a typical use failure rate of 6 pregnancies per 100 women per year of typical use compared to 0.2 pregnancies with perfect use (thought to be due to the 3 monthly requirements for re-injection and lack of compliance with this).

  - User dependent methods such as the condom, cap, diaphragm, combined oral contraceptive pill (COC) or progestogen-only contraceptive pill (POP) and fertility awareness based methods are not considered highly effective since the typical use incorporates user failure risks.

  - Patients should be provided with information about the types of contraception that are available, and have the opportunity to discuss the type that would suit them best.

- **Prescribing folic acid:**

  - Prescribers should consider prescribing folic acid supplements to all women of childbearing potential. Folic acid supplementation may decrease the general risk of neural tube defects but there is some evidence that it does not reduce the risk of birth defects associated with in utero.

Confirming absence of risk of pregnancy

- Where there are compelling reasons to suggest there is absence of risk of pregnancy, this should be specified on the risk acknowledgement form. These include:

  - Patients who are post-menopausal.
    - Women over 50 years old with at least 1 year history of amenorrhoea may be considered menopausal.
    - Consider using a Follicle Stimulating Hormone (FSH) test to diagnose menopause in women aged 40 to 50 years with menopausal symptoms, including a change in their menstrual cycle

  - Patients who have had a hysterectomy

- **Where the absence of risk of pregnancy is permanent** the Annual Risk Acknowledgement Form only needs to be completed once

- **Where the absence of risk is temporary** the next review date must be documented on the Annual Risk Acknowledgement Form.

Section C: New male patients under 55 years old started on valproate

- Initiation must ONLY be done by a Consultant Psychiatrist

- Two specialists need to independently consider and document in the patient's RiO progress notes and complete the Risk Acknowledgement form for men (Appendix 3) that there is no other effective or tolerated treatment for patients aged under 55 years before valproate is initiated.

- The risks of prescribing valproate should be discussed with the patient including possible risk of impaired fertility.

- Inform Medicines Safety Officer (kmpt.mso@nhs.net) if valproate is initiated in male patients under 55 years old

Section D: Existing male patients on valproate

- Men under 55 on valproate are advised to read the Patient Information Leaflet, provided with counselling and should be given the opportunity to discuss any concerns with their GP. If necessary, they should be offered a referral to a specialist to discuss their treatment options.

2.2 Who can be the second specialist signatory?

The Commission on Human Medicines (CHM), have advised a number of professionals can serve as the second specialist signatory. Within KMPT this includes:

- Consultant psychiatrists;

- Speciality and associate specialist doctors in psychiatry and neurology;

- Speciality doctors in psychiatry;

- Nurse ACP/NMP within their scope of practice.

2.3 Patients who lack capacity

- For patients who are assessed to lack capacity to consent to treatment then prescribing of valproate should be avoided. If a decision is made to initiate valproate then it should only be done on a KMPT inpatient ward after getting a second opinion from another Consultant and this should be documented in the patient's electronic RiO notes. A best interest meeting needs to be arranged for all patients without the capacity to make an informed decision. It is important to provide the information and advice on highly effective methods of contraception and on the use of valproate during pregnancy to their responsible person and make sure they clearly understand the content.

- If, after thorough consideration of the risks, it is concluded that the patient should continue to receive valproate after being transferred out of the inpatient ward, a clear risk-minimisation plan should be put in place and clearly documented in the patient's notes.

2.3 Patients who refuse information

- Occasionally patients may not wish to receive information when valproate is prescribed, or they may not currently be receptive to such information.

- In these circumstances, serious consideration should be given to delaying valproate treatment until the patient is willing and able to accept information about the risks posed by the drug.

- However, if the initiation of valproate is considered to be absolutely necessary, then the prescriber must complete the following actions:

    - Complete as much of the Annual Risk Acknowledgment Form (see appendix 2 or 3) as possible at the current time and add this to the patient's notes.

    - Ensure that another attempt to provide the information to the patient is made at the earliest possible opportunity.

    - Make an entry in the patient's electronic RiO notes stating why it was not possible to complete the full checklist and why it was considered necessary to prescribe the medication despite this.

    - Put a clear and practical risk-minimisation plan in place for both inpatients and patients in the community. For inpatients, this may involve putting them on an increased level of observation and restricting their leave from the ward until the valproate prescription has been stopped, or until the patient has received the necessary risk information about the drug. The plan must be clearly documented in the patient's notes.

2.4 Sharing information

- A copy of the Annual Risk Acknowledgment Form should be forwarded to the patient's GP along with their discharge summary or clinic letter.

- The GP should be asked to remind the patient about valproate's adverse effects at every consultation in which medication is discussed.

2.5 Monitoring and follow-up

- At all routine treatment reviews, prescribers must ensure that the benefits of valproate continue to outweigh the risks.

- For inpatients, the Annual Risk Acknowledgment Form must be completed when valproate is first prescribed and for any newly admitted patients who take the medication. The risks should be re-emphasised to the patient when they first go on leave, and when they are discharged.

- For outpatients, the checklist must be completed when valproate is first prescribed by the Responsible Consultant and reviewed at least annually for all women receiving long-term valproate. This is to ensure that their understanding of the risks and benefits is updated appropriately as their life plans change.

- If the patient's care is transferred back to the GP then there should be a plan agreed for the Responsible Consultant to continue with the annual reviews. A copy of the completed

Annual Risk Acknowledgment Form should be forwarded to the patient's GP along with their discharge summary or clinic letter.

- The Consultant needs to email the form to the medicine safety officer at kmpt.mso@nhs.net for every patient who is prescribed valproate and is of child bearing age in order for the Trust to keep a database of these details.

- Suspected side effects to valproate should be reported via the Yellow Card reporting scheme (https://yellowcard.mhra.gov.uk/) and recorded on the Trust incident reporting system.

3 ACTION FOR PHARMACISTS

- When valproate is dispensed for a patient on an inpatient ward, it is the responsibility of the pharmacist to ensure she is provided with a Patient card, unless they confirm that they already have one. For inpatients and community patients who are prescribed valproate, a patient card can be obtained from their CMHT pharmacist or locality KMPT pharmacy team.

  KMPT Pharmacy team (Canterbury) - 01227 812193
  KMPT Pharmacy team (Dartford and Medway) - 01322 622070
  KMPT Pharmacy team (Maidstone) - 01622 723219

- Any valproate prescribed on the inpatient wards that has been screened is annotated to highlight that its use for that patient is appropriate.

- The pharmacist must encourage the patient to read the card and enter their name and current date in the spaces provided.

- The pharmacist should remind all female patients of child-bearing age on valproate of the risks of taking it during pregnancy and the need for highly effective contraception.

- Remind patients that an annual review with the specialist will take place for as long as they are on valproate.

- Ensure the patients have received the Patient Guide (See link in Section A:new female patients)

4 FURTHER INFORMATION

- Further information can be accessed via Pregnancy Prevention Programme materials online. Available at:
  Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): new safety and educational materials to support regulatory measures in men and women under 55 years of age

- The link above provides printable versions of the communication materials mentioned in this document:

  - Patient Card – to be given by pharmacists to all female patients who are dispensed valproate medicines to inform them of the risks

- 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
- 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
- Risk Acknowledgement Form for women – 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
- Risk Acknowledgement Form for men – for new initiations, for the specialist and the secondary signatory to complete. 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

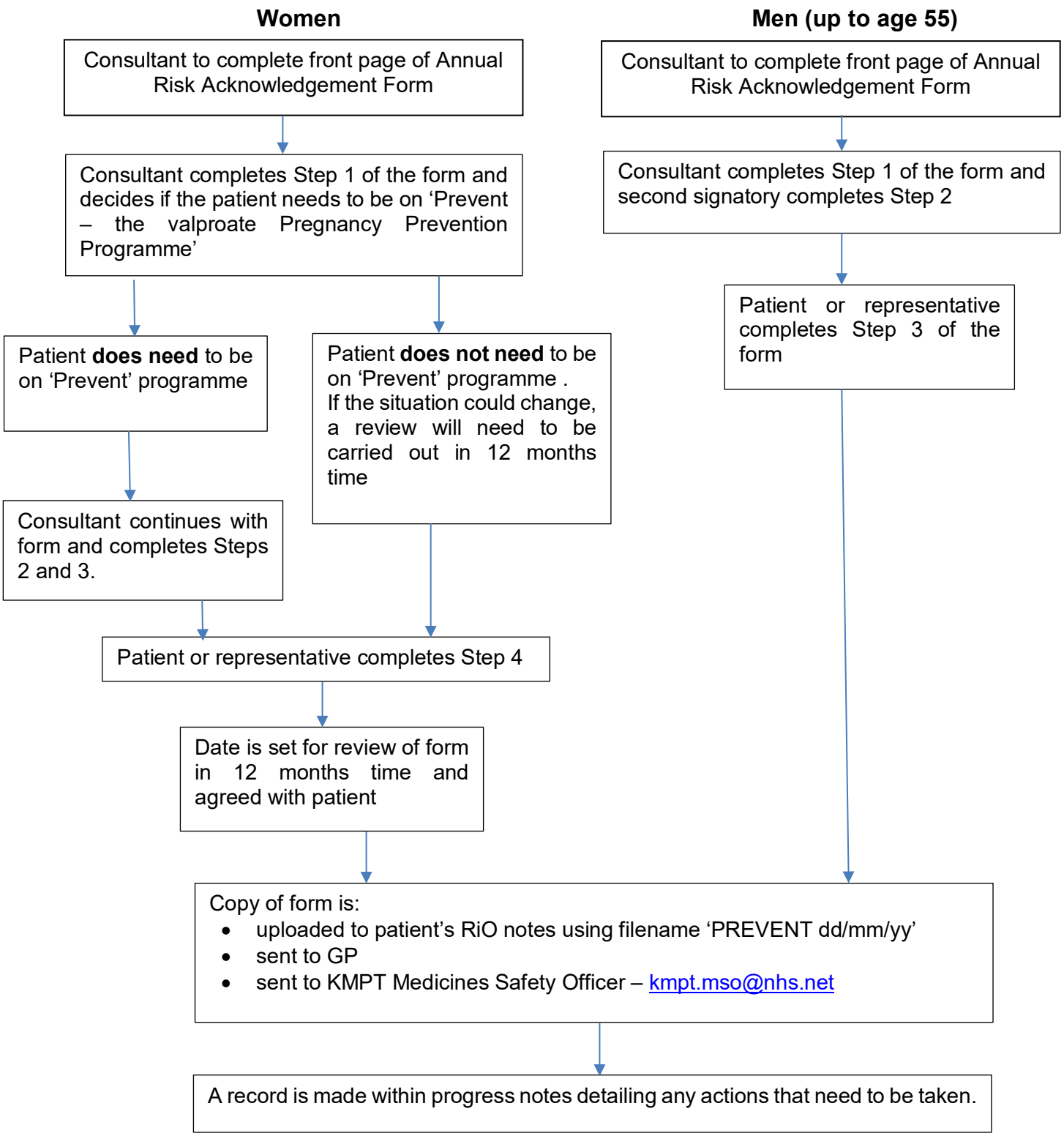
- Hard copies of these materials can be ordered by contacting the Sanofi Medical Information Department on 0845 372 7101, or via e-mail UK-Medicalinformation@sanofi.com

- An additional poster for dispensing pharmacies regarding actions to be taken when dispensing Valproate

- 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)

- Pregnancy testing information obtained from: Bastian LA and Brown HL. *Clinical manifestations and diagnosis of early pregnancy.* From "UpToDate®" clinical resource (Wolters Kluwer), Topic 440, Version 32.0. Topic last updated: 4th January 2016.

APPENDIX 1 GUIDE TO COMPLETING THE ANNUAL RISK ACKNOWLEDGMENT FORM



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

Children exposed to valproate during pregnancy have a high risk for congenital malformations and neurodevelopmental disorders which may lead to permanent disability.

Valproate should not be used in female patients aged under 55 years unless two specialists (specialist prescriber and countersigning specialist) independently consider and document, in this form, that there is no other effective or tolerated treatment. This form outlines the conditions of prevent - the valproate Pregnancy Prevention Programme and when these must be fulfilled.

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.

- This form is used to support and record the prescribing decision and, where applicable, discussion with the patient or their responsible person of the risks associated with the use of valproate during pregnancy and the measures needed to minimise the risks in female patients.
- The specialist prescriber must provide this form to female patients treated with valproate (Epilim, Depakote, Convulex, Episenta, Epival, Sodium Valproate, Syonell, Belvo & Dyzantil) – or to their "responsible person" i.e., a parent/legal guardian or person capable of giving consent on behalf of patients who are minors or without the capacity to make an informed decision, or a person acknowledging that the treatment is in the best interests of the patient.
- The decision of the countersigning specialist must be documented in step 2. A countersigning specialist is only required for patients 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.

Once completed, a copy of this form should be given to the patient or their responsible person and stored in their medical notes, it should also be shared with all healthcare professionals listed in the table below.

Name of patient:

Patient's date of birth:

Patient's NHS number:

Patient's hospital number:

Name and contact details of specialist prescriber:

Role and unique identifier:

Signature of specialist prescriber:

Date of signature:

Name of countersigning specialist:

Role and unique identifier:

Signature of countersigning specialist (if needed specialist prescriber can sign here to confirm that discussion with countersigning specialist has occurred):

Date of signature:

Name and address of patient's General Practitioner (GP):

Date form completed:

WARNING: Prescribing valproate to a woman of childbearing potential without the conditions of **prevent - the Pregnancy Prevention Programme** being fulfilled is contraindicated and represents an unlicensed use of the drug. Use of valproate during pregnancy for bipolar disorder, and during pregnancy for epilepsy (unless there is no other effective or tolerated treatment), are both unlicensed. This is the case even when treatment is based on an informed choice made by the patient.

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines listed.

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*):

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines listed.

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

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

Actions to be completed by the specialist prescriber to confirm the prescribing decision	**Initial to confirm all that apply**
• The patient's condition does not respond to other treatments or other treatments are not tolerated.	
• I have discussed the risks with the patient, and I consider the balance of benefits and risks to be favourable.	
• I have offered the patient a copy of the Patient Guide and they know where to get further information.	
• The patient is in the process of changing treatment away from valproate.	

To be completed by the countersigning specialist (can be completed by specialist prescriber following discussion with countersigning specialist if needed)	**Initial to confirm all that apply**
• I confirm that this patient should be treated with valproate.	
• The patient's condition does not respond to other treatments or other treatments are not tolerated.	
• The patient has been informed of the risks and I consider the balance of benefits and risks to be favourable.	
• The patient is in the process of changing treatment away from valproate.	

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

The risks must be discussed with the patient or their responsible person (if applicable), and the patient (or responsible person) must sign the subsequent section of this form to confirm they have discussed and acknowledge the risks of taking valproate during pregnancy.

Information to be discussed with the patient or their responsible person	**Initial to confirm you have discussed**
That their medication should be reviewed regularly (at least once a year) and their medication may need to be changed if their circumstances change, increasing the risks.	
That valproate can cause serious harm to an unborn baby if taken by a mother during pregnancy, which may lead to permanent disability. The overall risks in children exposed to valproate during pregnancy are: • an approximately 11% chance of physical birth defects • up to a 30% to 40% chance of neurodevelopmental disorders	
Explain the conditions of **prevent - the Pregnancy Prevention Programme** and why these must be fulfilled.	
The need for a negative (ideally serum) pregnancy test result before starting treatment with valproate and, if needed, further pregnancy tests at appointments thereafter.	
The need to use effective birth control (contraception), without interruption, throughout treatment with valproate.	
The need to consult their general practitioner (GP) for referral to the specialist as soon as they are planning pregnancy to ensure timely discussion and switching to another treatment before the child is conceived and before birth control (contraception) is discontinued.	
The need for the patient to contact their GP immediately, to be urgently referred to their specialist prescriber for an urgent review of their treatment in case of suspected or unplanned pregnancy.	
Explain the risks of stopping valproate without medical advice. Patients on valproate should not stop taking their medicine or change their dose unless they are told to do so by a specialist. This is because their condition may become worse, including an increase in seizures in patients treated for epilepsy and an increased risk of relapse in patients treated for bipolar disorder.	

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines listed.

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

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

Completing this section of the form confirms that you, the patient (or your responsible person), have discussed and acknowledge the risks of using valproate during pregnancy and the measures needed to reduce the risk with your specialist prescriber.

It is recommended that you keep a copy of this form which will also be added to your medical notes.

I have discussed the benefits and risks of valproate compared to other treatments with my specialist prescriber and I acknowledge that:	**Initial to confirm you acknowledge each item**
My medication should be reviewed regularly (at least once a year) and may need to be changed depending on my circumstances.	
Valproate can cause serious harm to an unborn baby if taken by a mother during pregnancy and may lead to permanent disability. The risks in children whose mothers took valproate during pregnancy are: • An approximately 11% chance of physical birth defects • Up to 30% to 40% of children may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory, or problems with development (behaviour and learning disorders) which can be seriously debilitating and/or permanent.	
I am aware of the need to have a negative pregnancy test before starting treatment with valproate and if needed, further pregnancy tests at subsequent appointments.	
I am aware of the need to use an effective method of birth control (contraception), without stopping or interruption, while taking valproate.	
The options for effective long-term methods of birth control (contraception) have been discussed (or a consultation has been planned with a professional who can give me advice).	
I need to consult my GP to be referred to my specialist prescriber as soon as I start thinking about becoming pregnant. This is to make sure I have time to switch to another treatment before I come off birth control (contraception).	
I should request an urgent appointment with my GP, to be urgently referred to my specialist prescriber, if I think I am pregnant.	
I have been offered a copy of the valproate Patient Guide and know where to find more information online using the QR code on the leaflet in the pack.	
I should not stop valproate or change the dose unless told to do so by my specialist as my condition may become worse, including an increase in seizures in patients treated for epilepsy and an increased risk of relapse in patients treated for bipolar disorder.	
Name of patient:	
Name of responsible person (if applicable):	
Signature of patient (or responsible person):	**Date:**

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines listed.

Risk Acknowledgement Form
FOR MALE PATIENTS STARTING VALPROATE

This form is used for new male patients starting a medicine containing valproate.

Valproate should not be started in male patients aged under 55 years unless two specialists consider and document that there is no other effective or tolerated treatment or the risk of infertility or potential risk of testicular toxicity do not apply.

This form applies to male patients aged under 55 years because this is the age group most likely to be affected by the risk of infertility and the potential risk of testicular toxicity. However, if these risks do not apply (e.g., the patient is permanently infertile), the countersigning specialist is not required, and the specialist prescriber should use this form to document the reason and record in the patients notes.

- This form is to support and record the discussion of risks with male patients aged under 55 years starting treatment with valproate or their responsible person or parents/care givers (if applicable).
- The specialist prescriber must provide this form to male patients aged under 55 years being started on valproate (Epilim, Depakote, Convulex, Episenta, Epival, Sodium Valproate, Syonell, Belvo & Dyzantil) – or to their "responsible person".
- In this instance, a responsible person is a parent/legal guardian or person capable of giving consent on behalf of patients who are minors or without the capacity to make an informed decision, or a person acknowledging that the treatment is in the best interests of the patient.
- The countersigning specialist must document their decision.

Once completed, a copy of this form should be given to the patient or their responsible person and stored in their medical notes, it should also be shared with all healthcare professionals listed in the table below.

Name of patient:

Patient's date of birth:

Patient's NHS number:

Patient's hospital number:

Name and contact details of specialist prescriber:

Role and unique identifier:

Signature of specialist prescriber:

Date of signature:

Name of countersigning specialist:

Role and unique identifier:

Signature of countersigning specialist (if needed specialist prescriber can sign here to confirm that discussion with countersigning specialist has occurred):

Date of signature:

Name and address of patient's GP:

Date form completed:

Step 1: Specialist prescriber and countersigning specialist: Document the prescribing decision

Actions to be completed by the specialist prescriber to confirm the prescribing decision	**Initial to confirm all that apply**
• The patient's condition does not respond adequately to other treatments or other treatments are not tolerated.	
• I have discussed the risks with the patient, and I consider the balance of benefits and risks to be favourable.	
• I have offered the patient a copy of the Patient Guide and they know where to get further information.	
• The risk of infertility or potential risk of testicular toxicity do not apply for the following reason(s):	

To be completed by the countersigning specialist prescriber (can be completed by specialist prescriber following discussion with countersigning specialist, if needed)	**Initial to confirm all that apply**
• Their condition does not respond to other treatments or other treatments are not tolerated.	
• They have been informed of the risks and I consider the balance of benefits and risks to be favourable.	

Step 2: Specialist prescriber: Explain the risks to the patient or responsible person

Information to be discussed with the patient or responsible person	**Initial to confirm you have discussed**
Fertility while on valproate • Valproate may cause infertility in some male patients. This can make it difficult to have a baby. • Male infertility may be reversible after valproate is stopped or after a dose reduction in some patients.	
Effects on male reproductive system • Some studies in male animals have shown valproate to have an adverse effect on parts of the male reproductive system. These include toxic effects on the testes (testicles). • The weight of the developing testes (testicles) was lower in young animals given valproate and it is unclear what this means for humans.	
Risks of stopping valproate without medical advice • Patients on valproate should not stop taking their medicine or change their dose unless they are told to do so by a specialist. • This is because their condition may become worse, including an increase in seizures in patients treated for epilepsy and an increased risk of relapse in patients treated for bipolar disorder.	

Step 3: To be completed by the patient or responsible person

Completing this section of the form confirms that you, the patient (or your responsible person), have discussed and acknowledge the risk of male infertility, and the toxic effect of valproate on the testes of animals using valproate.
It is recommended that you keep a copy of this form which will also be added to your medical notes.

I have discussed the benefits and risks of valproate compared to other treatments with my specialist prescriber and I acknowledge that:	**Initial to confirm you acknowledge each item**
• Valproate may cause infertility in some male patients and that this infertility may be reversible after valproate is stopped or after the dose is reduced for some patients.	
• There are animal studies showing that valproate may have an effect on testes (testicles) and it is unclear what this means for humans.	
• I should not stop valproate or change the dose unless told to do so by my specialist as my condition may become worse, including an increase in seizures in patients treated for epilepsy and an increased risk of relapse in patients treated for bipolar disorder. • If my condition becomes worse, I should contact my specialist straight away.	
• I have been offered the Patient Guide and know where I can access this information online using the QR code on the leaflet in the pack.	
Name of patient:	
Name of responsible person (if applicable):	
Signature of patient (or responsible person):	**Date:**