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Date of Birth:	
NHS number:	

Coventry & Warwickshire
Area Prescribing Committee

SHARED CARE AGREEMENT
Valproate▼/Valproic Acid▼
[In women and girls of childbearing potential]

SCA: Valproate medicines (licensed or unlicensed indications - epilepsy, manic episodes associated with bipolar disorder and migraine prophylaxis) MUST NOT be used in women and girls of childbearing potential (*menarche to post menopause)* unless the conditions of the **Pregnancy Prevention Programme (PPP)** are met, and *only* if other treatments are ineffective or not tolerated, as judged by an experienced specialist.

- These conditions are also applicable to female patients who are not sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy (which must be documented).
- There may be patients who lack capacity to understand the valproate guidance due to a learning disability. For these patients, documentation should be made of the capacity assessment and discussion of Valproate risks with carer so that a best Interest decision can be made regarding continuing or changing the treatment.

This shared care agreement primarily relates to the specific requirements to comply with the MHRA mandated Pregnancy Prevention Programme*. (MHRA Guidance 23 March 2018)*

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of valproate or valproic acid for epilepsy or bipolar disorder can be shared between the specialist and general practitioner (GP). GPs are **invited** to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.**

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the specialist initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

Specialist responsibilities

1. **For new patients:**
   a. Discuss the risks with the patient (or parent/caregiver/responsible* person). *Responsible person – see definition on the Risk Acknowledgement form (Specialist Page under the checklist)
   b. Only initiate treatment for epilepsy or bipolar disorder with valproate/valproic acid where other treatments are ineffective or not tolerated.
   c. A current negative serum pregnancy test result *must* be in place before prescribing.
   d. Highly effective contraception (see overleaf) must be in place *prior* to the first valproate/valproic acid prescription.
   e. Provide a copy of the Patient Guide to the patient (or parent/caregiver/responsible person).
2. **For all patients:**
   a. Undertake an annual review with the patient (or parent/caregiver/responsible person). This annual review must be evidenced by specialist and patient completion of the 'Annual Risk Acknowledgment Form'**.**
   b. Send a copy of the completed 'Annual Risk Acknowledgment Form' to the patient's GP.
   c. Confirm effective contraception (as defined overleaf) is in place, without interruption, throughout treatment. If this is not in place request the GP to arrange suitable contraception, and counsel the patient accordingly.
3. Urgently review within days (e.g. as soon as possible but less than 10 days) all patients referred back in case of unplanned pregnancy. Any patients wanting to plan a pregnancy should be reviewed in a timely manner (e.g. within 2 months). Pregnant patients taking valproate for *epilepsy* in pregnancy should be enrolled in the UK Epilepsy and Pregnancy Register. In *Bipolar disorder* - If a woman becomes pregnant, treatment with valproate must be switched and discontinued to another treatment.

Report any adverse events to the MHRA on a Yellow Card form (If in Coventry & Warwickshire Partnership Trust via the Clinical Governance Pharmacist – see Medicines Policy and associated guidance MMG20) and GP.

All females need to be assessed and must have the information about risks in pregnancy. If the clinician feels that there is a compelling reason to indicate that there is no risk of pregnancy then it may be agreed with the patient/parent/caregiver/responsible person that there is no current requirement for contraception. Any such risk discussion should be clearly documented.

General Practitioner responsibilities

1. Reply to the request for shared care (which must include a copy of a completed 'Annual Risk Acknowledgment Form') as soon as practicable by faxing back signed form. If declining the request, please indicate the reason for declining.
2. Retain a copy of the 'Annual Risk Acknowledgment Form' in the patient's records.
3. Provide or arrange for the patient to receive **highly effective contraception** (see overleaf). The need for effective contraception also applies to female patients who are not sexually active; unless there are compelling reasons to indicate that there is no risk of pregnancy. This must be documented.
4. The patient needs to understand the importance of continuous use of the contraception.
5. Prescribe the valproate/valproic acid at the dose recommended, from the agreed date.
6. Check that the patient has an up to date, signed; 'Annual Risk Acknowledgment Form' each time a prescription is issued.
7. Adjust the dose as advised by the specialist.
8. Ensure the patient is referred back to the specialist for review annually.
9. Unplanned pregnancy – contact the on-call neurologist or psychiatrist (ASAP) to arrange a referral back to the specialist for an urgent review of the patient's treatment.
10. Patients planning pregnancy - refer back to the specialist for a timely review (e.g. within 2 months) to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
11. Report any adverse events to the MHRA on a Yellow Card Form, the Specialist, and the relevant primary care Medicines Optimisation team.

Patient/parent/carer's/responsible person's role

1. Report to the specialist or GP if she does not have a clear understanding of the treatment.
2. Share any concerns in relation to treatment with valproate/valproic acid.
3. Understands the need for, and participate in regular (at least annual) review of treatment by the specialist. This includes joint completion with the specialist of an 'Annual Risk Acknowledgement Form'.
4. Inform the specialist or GP immediately for an urgent review of treatment in the case of suspected or inadvertent pregnancy or if wishing to plan a pregnancy.
5. Report any adverse effects or warning symptoms to the specialist or GP whilst taking valproate/valproic acid.
6. The patient may also choose to report any adverse drug reaction direct to the MHRA on a Yellow Card form, available at pharmacies, GP surgeries or from the Yellow Card hotline (Freephone 0808 100 3352 weekdays 10:00 to 14:00). The form can also be downloaded from http://yellowcard.mhra.gov.uk/

Back-up Advice and Support: See patient letter and/or other supporting information for contact details of clinician(s) initiating and stabilising patient prior to request for shared care.

SUPPORTING INFORMATION *(see SPC for complete details/specific guidance http://emc.medicines.org.uk)*

Pregnancy Prevention Programme: Valproate has a high teratogenic potential and children exposed in utero to valproate have a high (~10%) risk for congenital malformations and higher (30-40%) risk neurodevelopmental disorders.
Valproate is contraindicated in the following situations:

- In pregnancy. (Exception, in epilepsy only, if there is no suitable alternative treatment).
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled.

Conditions of Pregnancy Prevention Programme: The prescriber must ensure that:

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate in utero.
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of bipolar disorder or epilepsy.
- The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use ('Annual Risk Acknowledgement Form').

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children: The prescriber must ensure that:

- The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero.*

In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood.

Pregnancy test: Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception: Women of childbearing potential who are prescribed valproate must use effective contraception without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by a specialist: The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content.

Pregnancy planning: *Use in Bipolar:* If a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued, and if needed switched to an alternative treatment prior to conception and before contraception is discontinued.

Use in Epilepsy: If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy: If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure, as per the Summary of Product Characteristics, that:

- The Patient Card is provided with every valproate dispensation and that patients understand its content.
- Patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials: In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings provide guidance regarding use of valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. **A Patient Guide** and **Patient Card** should be provided to all women of childbearing potential using valproate.

An '**Annual Risk Acknowledgement Form'** needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist. There is a **Guide for Healthcare Professionals** to support their reviews.

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of bipolar disorder/epilepsy.

- These materials are available **electronically** at: https://www.gov.uk/guidance/valproate-use-by-women-and-girls under "Information"
- **Paper copies** may be requested through Sanofi's medical information department on: 0845 372 7101 or by email to UK-Medicalinformation@sanofi.com
- CWPT's internet (https://www.covwarkpt.nhs.uk/chapter-4-central-nervous-system) has links to the locally approved *'Risk Acknowledgement form'* as well as a *Valproate Guidance Summary* and *SOP*. All approved July 2018

Highly effective contraception is considered for regulatory purposes to be those user independent methods such as the long acting reversible contraceptives (LARC), copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS) and 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 requirement 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.
For children or for patients without the capacity to make an informed decision, provide the information and advice on highly effective methods of contraception and on the use of valproate during pregnancy to their parents/caregiver/responsible person and make sure they clearly understand the content.

At least one highly effective method of contraception (preferably a user independent form such as an intrauterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhoea she must follow all the advice on highly effective contraception.

Monitoring: Use the '**Risk Acknowledgement Form'** which must be completed before starting treatment and then annually. The form can be accessed on CWPT's internet or at the end of this document. This SCA focuses issues related to prescribing in female patients of childbearing potential. Additional monitoring should be undertaken as recommended in the SPC. CWPT also has approved guidance for monitoring antipsychotics and mood stabilisers, including valproate, which suggests recommended monitoring standards.

Specialist: Undertake an annual review with the patient or parent/caregiver/responsible person. This annual review must be evidenced by specialist and patient completion of the 'Annual Risk Acknowledgment Form'. A copy of the completed 'Annual Risk Acknowledgment Form' must be sent to the patient's GP.

GP: Ensure the patient is referred back to the specialist for review annually.

Cautions: This SCA focuses issues related to prescribing in female patients of childbearing potential. (Additional cautions should be considered as advised in the SPC). Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high (~10%) risk for congenital malformations and higher (30-40%) risk neurodevelopmental disorders.
Valproate is contraindicated in the following situations:

- In pregnancy. (Exception, in epilepsy only, if there is no suitable alternative treatment).
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the **lowest effective dose** and **divide the daily dose** valproate into several small doses to be taken throughout the day.
- The use of a **prolonged release formulation** may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.

All patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Side effects: See the current SPC for a comprehensive list of possible side-effects
All sodium valproate/valproic acid products currently have black triangle (▼) status.
All suspected adverse reactions should be reported to the MHRA.

Drug interactions (see also above under cautions): See the current SPC for a comprehensive list of possible drug interactions

Cost: This depends on the salt/brand/formulation and indicated dose. For guidance see the current BNF.

References:

1. https://bnf.nice.org.uk/ updated 2nd August 2018 **http://www.medicinesforchildren.org.uk/sodium-valproate-preventing-seizures**
2. MHRA 2015 Guidance: Valproate – Risks in Pregnancy: **https://www.gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormal-pregnancy-outcomes**
3. **MHRA 2018 Valproate Guidance and Information Resource links (Published 23rd March 2015, Updated 2nd August)** https://www.gov.uk/guidance/valproate-use-by-women-and-girls
4. MHRA 2018 Valproate Press Release 24th April https://www.gov.uk/government/news/valproate-banned-without-the-pregnancy-prevention-programme
5. MHRA 24th April 2018 Valproate medicines (Epilim▼, Depakote▼): contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met https://www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-contraindicated-in-women-and-girls-of-childbearing-potential-unless-conditions-of-pregnancy-prevention-programme-are-met
6. NICE Guidance Epilepsies: diagnosis and management. Updated April 2108 https://www.nice.org.uk/guidance/cg137
7. NICE Guidance Bipolar disorder: assessment and management. Updated April 2018 https://www.nice.org.uk/guidance/cg185

Coventry & Warwickshire
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Annual Risk Acknowledgement Form - VALPROATE HAS RISKS IN PREGNANCY

PATIENT Checklist: If you use valproate while you are pregnant, your child has significant risk of serious harm. This form confirms that you or your carer/parent/responsible person understands the risks of using valproate.

This form must be completed annually with the specialist caring for you

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

Part A. To be completed and signed by the valproate user and/or carer/parent or responsible person

I have discussed the following with my specialist and I understand:	
Why I need valproate rather than another medicine	☐ Yes
That I should visit a specialist regularly (at least once a year) to review whether valproate remains the best option for me	☐ Yes
The risks in children whose mothers took valproate during pregnancy are: • 1 out of 10 children will have physical birth defects • 3 to 4 out of 10 children will have early developmental problems that can lead to significant learning disabilities	☐ Yes
That I have had a pregnancy test (if advised by my doctor/specialist)	☐ Yes
Why I must use **effective** contraception, without stopping or interruption, at all times while taking valproate	☐ Yes
The options for **effective** long-term contraception (or a consultation has been planned with a professional who can give me advice)	☐ Yes
The need to consult my specialist or GP as soon as I start thinking about becoming pregnant. This is to make sure I have time to discuss my treatment options including a switch to another treatment before I come off contraception	☐ Yes
That I should request an urgent GP appointment if I think I am pregnant	☐ Yes
That I have a copy of the Patient Guide and know where to find more information	☐ Yes
In case of pregnancy, I confirm that: • I have considered and discussed options for switching treatment • I am fully aware of the risks and have the opportunity to have counselling about the risks	☐ Yes

Long-term contraceptives are strongly recommended such as a coil (copper intrauterine device [IUD] or levonorgestrel intrauterine system) and contraceptive implant (progestogen-only implant), or sterilisation.

Contraceptive currently used: ……

Name of valproate user: ……

Name of parent/caregiver/responsible person (if applicable): ……

Signature: ……. **Date**: …….

This form expires 12 months from this date - a new form should be completed at each annual review

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 that appear.

Cont'd overleaf

SPECIALIST Checklist: If a woman uses valproate while she is pregnant, her child may be harmed. Valproate (licensed or unlicensed indications) may only be prescribed in girls and women of childbearing potential*/** if the conditions of Prevent – The Valproate Pregnancy Prevention Programme are fulfilled. This form confirms that you have explained the risks of using valproate.

You must complete this form annually with your patient.

**A female who has not passed menopause and is capable of becoming pregnant.*

***This also applies to female patients who are not sexually active - unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy. This must be documented.*

****There may be patients who lack capacity to consent to the risks with valproate and the Pregnancy Prevention Programme. For these patients, documentation should be made of the capacity assessment and discussion of valproate risks with parent/caregiver/responsible person regarding continuing or changing the treatment. A Best Interest Meeting should be held (and documented) for adults.*

Name of valproate user: …….. **Ward/Unit/Team**…….

Name of parent/carer/responsible person (if applicable): ……..

Name, role, and signature of specialist: ……

Name of valproate user's GP: …… **Date:** ……

Part B. To be completed and signed by the specialist

I confirm that the above-named patient needs valproate because:

- her condition does not respond adequately to other treatments, or ☐
- she does not tolerate other treatments ☐

I confirm that I have discussed the following information with the person named above:

Valproate must not be used during pregnancy (except in rare situations in epilepsy for patients who are resistant or intolerant to other treatments. Note – pregnant patients taking valproate for epilepsy in pregnancy should be enrolled in the UK Epilepsy and Pregnancy Register.)	☐ Discussed
The overall risks in children exposed to valproate during pregnancy are: • an approximately 10% chance of birth defects • a 30 to 40% chance of a wide range of early developmental problems that can lead to learning disabilities.	☐ Discussed
The conditions of the pregnancy prevention programme must be fulfilled	☐ Discussed
The need for regular (at least annual) review of the need to continue valproate treatment by a specialist	☐ Discussed
The need for **effective** contraception, without interruption, throughout treatment with valproate. **This must be arranged BEFORE** the prescription for valproate is issued.	☐ Discussed
The need to arrange an appointment with her specialist as soon as she is planning pregnancy to ensure timely discussion and switching to an alternative treatment before conception and before stopping contraception.	☐ Discussed
The need to contact her GP immediately for an urgent review of her treatment in case of suspected or inadvertent pregnancy.	☐ Discussed
The patient or parent/caregiver/responsible person has a copy of the patient guide	☐ Discussed
The need for a negative serum pregnancy test result at start and if needed thereafter **It is essential that pregnancy is excluded** via a serum pregnancy test **BEFORE** prescribing.	☐ Discussed

In case of pregnancy, I confirm that:

- We have discussed options for switching treatment ☐
- She is fully aware of the risks of pregnancy, has opportunity for counselling about risks ☐

The specialist must provide this form to girls and women of childbearing potential treated with valproate (Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Orlept, Syonell, Valpal) - or to their "responsible person": 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 person acknowledging that the treatment is in the best interests of the patient.

A copy of the completed and signed form must be kept/recorded by the specialist and prescriber.

Copies of the completed and signed form MUST be given to the patient (or carer/parent/responsible person) and also sent to their GP.