Effective Shared Care Agreement (ESCA)

Sodium valproate/Valproic acid medicines in women and girls of childbearing potential (all indications)

ESCA: For the use of sodium valproate/valproic acid medicines which are contraindicated in women and girls of childbearing potential **unless** conditions of Pregnancy Prevention Programme are met. Use in men and women of non-child bearing potential is not subject to this shared care.

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of sodium valproate/valproic acid medicines **in women and girls of childbearing potential** for epilepsy or bipolar disorder or any unlicensed/off-label indication can be shared between the specialist and general practitioner (GP) if conditions of Pregnancy Prevention Programme are met. You are **invited** to participate however, if you do not feel confident to undertake this role, then you are 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.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care will be explained to the patient by the specialist initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients with epilepsy or bipolar disorder or any unlicensed indication are usually under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

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

RESPONSIBILITIES and ROLES

Specialist responsibilities
1. Confirm the diagnosis of epilepsy or bipolar disorder or any unlicensed/off-label indication (please list - _____)
2. Specialist to complete the Risk Acknowledgement Form with the patient (or their parent/caregiver/responsible person) to sign at initiation and at treatment reviews at least annually. The Risk Acknowledgement Form can be found by accessing: https://www.gov.uk/guidance/valproate-use-by-women-and-girls 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. Ensure that all patients receive the 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 (all brands and branded generics).
4. Ensure that the patient has been included on the Pregnancy Prevention Programme, or clearly document reasons why this is not considered necessary in cases where there is no risk of pregnancy.
5. Discuss the potential benefits, treatment side effects, and possible drug interactions with the patient
6. Ask the GP whether he or she is willing to participate in shared care before initiating therapy so that appropriate follow on prescribing arrangements can be made.
7. Do baseline monitoring prior to initiation of sodium valproate/valproic acid medicines
8. Initiate treatment and stabilise dose of sodium valproate/valproic acid medicines
9. Review the patient's condition and monitor response to treatment regularly
10. A written summary to be sent promptly to the GP i.e. within 10 working days of a hospital outpatient review or inpatient stay
11. If a patient becomes pregnant while taking valproate medication and the specialist team are notified (either via the patient, patients representation, patients GP), the patients must be seen by the specialist within 2 weeks of notification. The patient should not stop taking their valproate medication.
12. Report serious adverse events to the MHRA via Yellow Card Scheme https://yellowcard.mhra.gov.uk
13. Ensure clear backup arrangements exist for GPs, for advice and support (please complete contact details in the ESCA)
14. Respond appropriately if an urgent referral from GP is received

General Practitioner responsibilities						
1. Ensure the Risk Acknowledgement Form has been completed and is in date. Ensure that an annual referral date is agreed and relayed to the patient, with an alert on the patient record. The Risk Acknowledgement Form can be found by accessing: https://www.gov.uk/guidance/valproate-use-by-women-and-girls						
2. Ensure that patients have received the Patient Guide.						
3. Ensure that the patient has been included on the Pregnancy Prevention Programme or there are clearly document reasons why this is not considered necessary in cases where there is no risk of pregnancy.						
4. Reply to the request for shared care as soon as practicable i.e. within 10 working days.						
5. Prescribe sodium valproate/valproic acid medicines at the dose recommended.						
6. Adjust the dose as advised by the specialist.						
7. In the patient's notes, using the appropriate read code listed below, denote that the patient is receiving treatment under a shared care agreement						
GP Prescribing System	**Read Code**	**Description**		**GP Prescribing System**	**Read Code**	**Description**
EMIS and Vision	8BM5.00	Shared care prescribing		SystmOne	XaB58	Shared care
8. If the patient is taking valproate medication, please ensure that the records are update with relevant system read code to support their care.						

GP Prescribing System	Valproate Read Code	Description
System One	Y1b25	Advice on risk harm to foetus from maternal Sodium Valproate during pregnancy
EMIS	EMISNQPR472	Pregnancy prevention programme form signed by patient
	EMISNQCO292	Contraceptive advice for patients on valproate for epilepsy
Vision	6110	Contraceptive advice for patients with epilepsy

General Practitioner responsibilities (continued)
9. Monitor patient's response to treatment; make dosage adjustments if agreed with specialist
10. Report to and seek advice from the specialist or clinical nurse specialist on any aspect of patient care that is of concern to the GP, patient or carer and may affect treatment
11. Refer to specialist urgently if condition deteriorates or if patient is planning on becoming pregnant/unplanned suspected pregnancy
12. If the patient becomes pregnant while taking valproate medication, the specialist team must be notified and the patient must be seen by the specialist within 2 weeks of notification. The patient should not stop taking their valproate medication.
13. Report serious adverse events to specialist and MHRA via the Yellow Card Scheme https://yellowcard.mhra.gov.uk
14. Stop treatment on advice of specialist

Patient's role
1. Ensure that the Patient Guide has been received and the Annual Risk Acknowledgement Form has been completed.
2. If considering pregnancy or become pregnant – please contact the specialist, clinical nurse specialist or GP as soon as possible.
3. Ensure that the annual review date is agreed and attended; add an alert to personal calendar(s).
4. Report to the specialist, clinical nurse specialist or GP if she does not have clear understanding of the treatment

5.	Attend regular outpatient appointments with the specialist
6.	Share any concerns in relation to treatment with sodium valproate/valproic acid medicines with the specialist, clinical nurse specialist or GP
7.	Report any adverse effects to the specialist or GP whilst taking Sodium valproate/Valproic acid medicines (all brands and branded generics)

SUPPORTING INFORMATION

<table>
<tr><td>Preparations
Indication and licencing</td><td colspan="3">
<table>
<tr><th>Brand</th><th></th><th>Epilepsy</th><th>Bipolar disorder</th></tr>
<tr><td>Sodium valproate</td><td>Sodium valproate</td><td>☑</td><td></td></tr>
<tr><td>Epilim</td><td>Sodium valproate</td><td>☑</td><td></td></tr>
<tr><td>Epilim Chrono</td><td>Sodium Valproate and Valproic Acid Controlled Release</td><td>☑</td><td></td></tr>
<tr><td>Epilim Chronosphere MR</td><td>Sodium Valproate and Valproic Acid modified release granules</td><td>☑</td><td></td></tr>
<tr><td>Episenta modified-release</td><td>Sodium Valproate prolonged-release capsule and prolonged-release granules</td><td>☑</td><td>☑</td></tr>
<tr><td>Episenta solution for injection</td><td>Sodium Valproate</td><td>☑</td><td></td></tr>
<tr><td>Epival CR</td><td>Sodium valproate prolonged-release</td><td>☑</td><td>☑</td></tr>
<tr><td>Depakote</td><td>Valproic acid (as Valproate semisodium)</td><td></td><td>☑</td></tr>
<tr><td>Convulex</td><td>Valproic acid</td><td>☑</td><td></td></tr>
</table>
</td></tr>
<tr><td>MHRA Category 2</td><td colspan="3">The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency and treatment history</td></tr>
<tr><td colspan="4">Dosage and Administration</td></tr>
<tr><td>Adults</td><td colspan="2">For Epilepsy:

Dosage should start at 600 mg daily increasing by 200 mg at three-day intervals until control is achieved.
This is generally within the dosage range 1000 – 2000 mg per day, i.e. 20 – 30 mg/kg/day body weight.
Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.</td><td>Manic episodes in bipolar disorder:

The daily dosage should be established and controlled individually by the treating physician.
The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg valproate/kg body weight has also shown an acceptable safety profile.
Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect.
The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient.
The mean daily dose usually ranges between 1000 – 2000 mg valproate.
Patients receiving daily doses higher than 45 mg/kg/day body weight should be carefully monitored.
Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.</td></tr>
<tr><td>Children <u>over</u> 20 kg</td><td colspan="2">Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20 – 30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.</td><td rowspan="2">Children and adolescents
The safety and efficacy of Depakote for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years</td></tr>
<tr><td>Children <u>under</u> 20kg</td><td colspan="2">20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be</td></tr>
</table>

	monitored.	

Renal Impairment	It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading	
Hepatic impairment	Avoid if possible as hepatotoxicity and hepatic failure may occasionally occur within the first 6 months of treatment. Avoid in active liver disease	
Contra-indications	• **In pregnancy unless there is no suitable alternative treatment** • **In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled** • **Acute porphyrias** • Active liver disease • Personal or family history of severe hepatic dysfunction, especially drug related. • Patients with known urea cycle disorders • Hypersensitivity to the active substance or to any of the excipients Porphyria • Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder	
Special precautions	• Liver dysfunction – monitor liver function • Systemic lupus erythematosus • Suicidal ideation and behaviour - Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge • NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations • The concomitant use of valproic acid/sodium valproate and carbapenem agents is not recommended • Pancreatitis: Patients should be advised to consult their doctor immediately if they develop symptoms suggestive of pancreatitis (e.g. abdominal pain, nausea and vomiting, monitor serum amylase) • Weight gain: Valproate very commonly causes weight gain, which may be marked and progressive. All patients should be warned of this risk at the initiation of therapy and appropriate strategies adopted to minimise weight gain • Patients with known or suspected mitochondrial disease: POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders • Alcohol intake is not recommended during treatment with valproate	
Side Effects	Very common	Nausea, tremor
	Common	liver injury/ dysfunction, vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea confusional state, hallucinations, aggression, agitation, disturbance in attention, anaemia, thrombocytopenia, hyponatraemia, weight increased, hypersensitivity, transient and or dose related alopecia (hair loss), nail and nail bed disorders, dysmenorrhea, haemorrhage, deafness

Monitoring	Pre-treatment assessment	Risk Acknowledgement Form Pregnancy test – if suspected Liver function – baseline Renal function – baseline Full blood count and U&E's – baseline Serum urea– baseline Serum amylase– baseline Baseline weight Suicidal ideation and behaviour
	After commencing treatment In most cases if symptomatic	Annual Risk Acknowledgement Form Pregnancy test – if suspected Liver function before therapy and during first 6 months especially in high risk patients Renal function Full blood count and U&E's Serum urea Serum amylase Baseline weight Suicidal ideation and behaviour

Drug Interactions
(significant interaction as outlined in BNF, please see BNF and SPC for more detail)

Valproate has the following interaction information:

Medication	Severity of interaction	Evidence for interaction	Notes	
Acetazolamide	Severe	Study	Acetazolamide potentially increases the risk of toxicity when given with valproate.	
Bupropion	Severe	Study	Valproate increases the exposure to bupropion.	
Ertapenem	Severe	Anecdotal	Ertapenem decreases the concentration of valproate.	Manufacturer advises avoid
Fosphenytoin	Severe	Study	Valproate affects the concentration of fosphenytoin and fosphenytoin decreases the concentration of valproate.	
Glycerol phenylbutyrate	Moderate	Theoretical	Valproate potentially opposes the effects of glycerol phenylbutyrate.	
Guanfacine	Moderate	Study	Guanfacine increases the concentration of valproate.	Manufacturer advises monitor and adjust dose.
Imipenem	Severe	Anecdotal	Imipenem decreases the concentration of valproate.	Manufacturer advises avoid
Lamotrigine	Severe	Study	Valproate increases the exposure to lamotrigine.	Manufacturer advises adjust lamotrigine dose and monitor rash.
Meropenem	Severe	Anecdotal	Meropenem decreases the concentration of valproate.	Manufacturer advises avoid
Paliperidone	Moderate	Study	Valproate slightly increases the exposure to paliperidone.	Manufacturer advises adjust dose.
Phenobarbital	Moderate	Study	Phenobarbital decreases the concentration of valproate and valproate increases the concentration of phenobarbital.	Manufacturer advises monitor and adjust dose
Phenytoin	Severe	Study	Valproate affects the concentration of phenytoin and phenytoin decreases the concentration of valproate.	
Pivmecillinam	Severe	Anecdotal	Valproate increases the risk of side-effects when given with pivmecillinam.	Manufacturer advises avoid.
Primidone	Severe	Study	Valproate affects the concentration of primidone.	Manufacturer advises monitor and adjust dose
Propofol	Severe	Theoretical	Valproate potentially increases the concentration of propofol.	Manufacturer advises adjust dose.
Quetiapine	Moderate	Study	Valproate potentially increases the risk of neutropenia when given with quetiapine.	
Ritonavir	Severe	Anecdotal	Ritonavir is predicted to decrease the concentration of valproate.	
Rufinamide	Moderate	Study	Valproate increases the exposure to rufinamide.	Manufacturer advises adjust rufinamide dose.
Selexipag	Unknown	Theoretical	Valproate is predicted to increase the exposure to selexipag.	
Sodium oxybate	Moderate	Study	Valproate increases the exposure to sodium oxybate.	Manufacturer advises adjust sodium oxybate dose
Sodium phenylbutyrate	Moderate	Anecdotal	Valproate potentially decreases the effects of sodium phenylbutyrate.	
Topiramate	Severe	Study	Topiramate increases the risk of toxicity when given with valproate.	
Zidovudine	Moderate	Study	Valproate slightly increases the exposure to zidovudine.	

*Please refer to SPC or BNF for full list of interactions

References

- MHRA Drug Safety Update - Valproate medicines (Epilim▼, Depakote▼): contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met. April 2018. Available from: 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 [Accessed January 2019]
- MHRA Drug Safety Update - Valproate medicines (Epilim▼, Depakote▼): Pregnancy Prevention Programme materials online. May 18 Available from: https://www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-pregnancy-prevention-programme-materials-online [Accessed January 2019]
- BNF Online.

Effective Shared Care Agreement (ESCA)

Sodium valproate/Valproic acid medicines in women and girls of childbearing potential (all indications)

For the use of Sodium valproate/Valproic acid medicines (all brands and generics) which are contraindicated in women and girls of childbearing potential **unless** conditions of Pregnancy Prevention Programme are met. Use in men and women of non-child bearing potential is not subject to this shared care.

Please refer to BSSE APC formulary website for complete document.

BACK-UP ADVICE AND SUPPORT (To be completed by Specialist team)

Trust	Contact details	Telephone No.	Email address:
	Consultant:-		
	Specialist Nurse		

Brand		Epilepsy	Bipolar disorder	Select brand
Sodium valproate	Sodium valproate	☑		
Epilim	Sodium valproate	☑		
Epilim Chrono	Sodium Valproate and Valproic Acid Controlled Release	☑		
Epilim Chronosphere MR	Sodium Valproate and Valproic Acid modified release granules	☑		
Episenta modified-release	Sodium Valproate prolonged-release capsule and prolonged release granules	☑	☑	
Episenta solution for injection	Sodium Valproate	☑		
Epival CR	Sodium valproate prolonged-release	☑	☑	
Depakote	Valproic acid (as Valproate semisodium)		☑	
Convulex	Valproic acid	☑		

If being used off-label or unlicensed indication. Please list……..

Pregnancy Prevention Programme condition	Specialist signature	Date discussed	
Patient (patients parent/caregiver/responsible person) has been told and understands the risks of use in pregnancy and has signed a Risk Acknowledgement Form (Appendix 2)			Please share Risk Acknowledgement Form with patient and their GP
Patient is on highly effective contraception (User independent methods such as long acting reversible contraceptives (LARC), copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS) and progestogen-only implant (IMP) and female sterilisation.)			Name of highly effective contraceptive: _____
Patient sees their specialist at least every year.			Date of next appointment:

If Pregnancy Prevention Programme conditions considered not necessary	Specialist signature	Date discussed	
Risks explained to patient (parent/caregiver/responsible person), but Pregnancy Prevention Programme conditions not considered necessary due to a compelling reason to indicate there is no risk of pregnancy			Please state reason:

Patient's name	Date of birth	Home Address	Hospital Number
			NHS Number

Patient

Name (please print)_____Signature_____Date_____

Hospital Specialist/Consultant
Name (please print)_____Signature_____Date_____

To be completed by the General Practitioner:

I agree to participate in this shared care agreement for the treatment of the above named patient with *Sodium valproate/Valproic acid medicines) in women and girls of childbearing potential for epilepsy or bipolar disorder or unlicensed/off-label indication. Please list indication being treated……*

General Practitioner
Name (please print)_____Signature _____Date_____

Please keep a copy of this agreement for your own records and forward the original to the above named Consultant.

In the patient's notes, using the appropriate Read Code listed below, denote that the patient is receiving treatment under a shared care agreement.

GP Prescribing System	Read Code	Description		GP Prescribing System	Read Code	Description
EMIS and Vision	8BM5.00	Shared care prescribing		SystmOne	XaB58	Shared care