Valproate semisodium *(Depakote®)* (Amber)

for the treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated.

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines how responsibility for prescribing valproate semisodium for the treatment of manic episode in bipolar disorder (when lithium is contraindicated or not tolerated), might be shared between 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 doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

This shared care is intended to apply to patients who have been initiated on treatment (and who have been assessed as benefiting) by a specialist in the care of patients with bipolar, in accordance with the guidance on Bipolar disorder (the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care) from NICE Clinical Guideline 185

Valproate should not be routinely prescribed to women of child-bearing potential. If there is no effective alternative, the risks of taking valproate during pregnancy, and the importance of using adequate contraception, should be explained.

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

RESPONSIBILITIES and ROLES (insert as much additional text as appropriate)

	Specialist responsibilities
1	**Initiate treatment and prescribe the first 3 months of treatment of valproate semisodium.**
2	**Discuss the benefits and side effects of treatment with the patient.**
3	**Ask the GP whether he or she is willing to participate in shared care (using the approved shared care agreement and signed shared care agreement signature sheet for valproate semisodium). Discuss the shared care arrangement with the patient & obtain their consent (verbal is fine). Document in patients electronic records. If patient declines shared care, document this too.**
4	**Supply GP with summary within 14 days of a hospital out-patient review or in-patient stay.**
5	**Review the patient's condition and monitor response to treatment regularly where indicated.**
6	**Give advice to the GP on when to adjust the dose / stop treatment.**
7	**Report adverse events to the MHRA & GP.**
8	**Ensure that clear backup arrangements exist for GPs to obtain advice and support.**
9	Assess patient, establish the diagnosis and develop a care plan. Ensure care plan contains correct contact details of care co-ordinator/key worker and specialist. Forward copy of care plan to the GP.
10	To undertake physical health screen and assessment for the first 3 months.
11	To provide the patient with verbal and written information on valproate semisodium including a patient information leaflet (PIL). Information on mental health conditions, treatments and medication can be found at: http://www.choiceandmedication.org/awp/
12	Provide counselling to patient and carer about implications of diagnosis; include written information about signs and symptoms, course, prognosis and treatments, local care and support groups, financial and legal advice.
13	The choice and formulation of drug for mania should be a joint decision between the patient, (discuss with carer where patients lack capacity) and the specialist taking into consideration the risks and benefits of the treatment (including the relative potential of valproate semi-sodium to cause side-effects) including any action to be taken should side effects occur.
14	To ensure the patient is fully informed about their treatment - for women of child bearing potential this should also include a discussion about plans for pregnancy as per NICE CG 45 (Antenatal and postnatal mental health) for guidance on the management of bipolar disorder during pregnancy and the postnatal period and in women and girls of childbearing potential. Effective contraception should also be discussed.
15	Patients on valproate semi-sodium, and their carers, should be advised how to recognise the signs and symptoms of blood and liver disorders and to seek immediate medical help if these develop.
16	Ensure that arrangements for appropriate blood tests have been made. Blood tests may be taken at the GP surgery providing appropriate communication with the GP and the GP is in agreement with this. The Specialist is responsible for the interpretation and monitoring of these blood test results for the first 3 months of treatment.
17	Review results of any baseline tests and relay any abnormal findings to the GP with appropriate advice.
18	Review concurrent medication for potential interaction prior to initiation of valproate semi-sodium, including medication patient receives from the GP and purchases OTC or on-line.
19	To review the patient and treatment at least once a year until the patient is discharged from the mental health

service where this is possible.
20 To review patient / provide advice as requested via the GP or Primary Care Liaison Service as necessary
21 Discuss appropriate lifestyle issues e.g. healthy eating, with the patient.
22 Communicate promptly with the GP when treatment is changed.
23 Inform GP if any appointments are not attended.
24 Any verbal communication between primary care and the specialist team should be confirmed in writing

General Practitioner responsibilities
1 **Reply to the request for shared care as soon as practicable (preferably within 3 weeks of receipt of request) using the shared care agreement signature sheet for valproate semisodium.**
2 **Prescribe medicine at the dose recommended after the first 3 months.**
3 **Ensure compatibility with other concomitant medication.**
4 **Refer promptly to specialist when any loss of clinical efficacy is suspected (e.g. worsening of disease-related symptoms, new symptoms suggestive of disease recurrence or progression) or intolerance to therapy occurs.**
5 **Report to and seek advice from the specialist on any aspect of patient care that is of concern to the GP and may affect treatment.**
6 **Adjust dose / stop drug on the advice of the specialist.**
7 **Report adverse events to the specialist and MHRA.**
8 If the GP decides not to prescribe valproate semisodium, it should still be added to the patients repeat medication as a "non issued' item for information and safety purposes. The quantity should be set to *0 or 1. On the dose line it should read: 'Hospital prescribing only. Do not prescribe'. This should also be done during the stabilisation period before GP takes over the prescribing (valproate semisodium is an enzyme inhibitor and may interact with other medication the patient is taking).
9 Monitor response to treatment including changes in symptoms and behaviour.
10 Monitor patients physical health as detailed under monitoring. A copy of the results should be sent to the care coordinator and psychiatrist (to file in the secondary care records).
11 Once the patient has been discharged, advice may be sought from the Patient Care Liaison Service on any aspect of patients mental health that is of concern to the GP.
12 Monitor patients overall health and compliance with medication. Ask patient / carer about particular problems e.g. side effects, concerns about treatment.
13 To notify specialist of any relevant changes in other medications or clinical status.
14 To ensure that practice staff are aware that valproate semisodium refers to Depakote® and not Epilim; Patients with bipolar disorder and epilepsy are distinct populations. Particular caution when transcribing to patient medication records as products have different license indications and different strengths available.

Primary Care Liaison Service (PCLS) responsibilities
1. Accept referrals by registered GPs in line with DoH guidance.
2. To advise the GP on appropriate action regarding any issues they may have on patient's management regarding shared care.
3. To try and resolve the issue(s) raised by the GP or to refer to the specialist team as appropriate.
4. Rapid & prioritised specialist mental health assessment with recommendation/s for care & treatment within multiple care pathways.
5. Determination of the nature & severity of mental health needs with consequent sign posting and pathway facilitation
6. Provide rapid and accessible ongoing support & advice to the non-specialist workforce

Patient's role
1 Attend all appointments with GP and specialist.
2 Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
3 Share any concerns in relation to treatment with medicine.
4 Inform specialist or GP of any other medication being taken, including over-the-counter or those purchased on-line.
5 Report any adverse effects to the specialist or GP whilst taking the medicine.

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No.	Bleep:	Fax:	Email address:
Specialist:				
Care co-ordinator				
Primary Care Liaison Service Sandalwood Court, Swindon 8am – 8pm then Intensive service	01793 835787		01793 836817	

SUPPORTING INFORMATION

Summary of condition (NICE CG 185)

Bipolar disorder is a potentially lifelong and disabling condition characterised by episodes of mania (abnormally elevated mood or irritability and related symptoms with severe functional impairment or psychotic symptoms for 7 days or more) or hypomania (abnormally elevated mood or irritability and related symptoms with decreased or increased function for 4 days or more) and episodes of depressed mood. It is often comorbid with other disorders such as anxiety disorders, substance misuse, personality disorders and attention deficit hyperactivity disorder (ADHD).
The peak age of onset is 15–19 years, and there is often a substantial delay between onset and first contact with mental health services. The lifetime prevalence of bipolar I disorder (mania and depression) is estimated at 1% of the adult population, and bipolar II disorder (hypomania and depression) affects approximately 0.4% of adults.

Licensed indications

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to valproate semisodium (Depakote) for acute mania.

Valproate semisodium should not be routinely prescribed for women of child bearing potential.

Expected / established place in local treatment pathway

Valproate semisodium is licensed to be prescribed where lithium is contraindicated or not tolerated. Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose which produces the desired clinical effect. If treatment is stopped the dose should be reduced gradually over at least 4 weeks.

Dosage and administration

For adults (18 years and over)

- The initial recommended daily dose is 750 mg daily in 2 to 3 divided doses, increased according to response.
- The mean daily dose usually ranges between 1000mg and 2000mg valproate semisodium.
- Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored.
- In clinical trials a starting dose of 20 mg valproate/kg body weight has also shown an acceptable safety profile.

Tablets should be swallowed whole with a drink of water, and not crushed or chewed.

Contra-indications and precautions for use

- Active liver disease
- Personal or family history of severe hepatic dysfunction, drug related
- Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
- Porphyria
- Care must be taken not to confuse valproate semisodium (Depakote) with sodium valproate (Epilim). Patients with bipolar disorder and epilepsy are distinct populations.
- Discontinuation should normally only be done under the supervision of a specialist in a gradual manner (over at least 4 weeks). This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.
- **Liver dysfunction:** Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Clinical symptoms are essential for early diagnosis.
  - Non specific symptoms, usually of sudden onset, include asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- **Pancreatitis:** which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).
- **Haematological:** Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding.

- **Renal insufficiency:** In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring
- **Systemic lupus erythematosus:** Although immune disorders have only rarely been noted during the use of valproate semisodium, the potential benefit of this drug should be weighed against its potential risk in patients with systemic lupus erythematosus.
- **Hyperammonaemia:** When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate semisodium.
- **Weight gain**: Valproate semisodium very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it.
- **Pregnancy:** Valproate semisodium should not be routinely prescribed for women of child bearing potential (See SPC for full details).
- **Diabetic patients:** Valproate semisodium is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Special recommendations
Pregnancy

- Valproate increases the risk of neural tube defects (mainly spina bifida and anencephaly) from around 6 in 10,000 pregnancies in the general population to around 100 to 200 in 10,000. It also has effects on the child's intellectual development. Many pregnancies are unintended and/or not confirmed until after the 28th day (when the neural tube closes) so care is needed when prescribing the drug.

- Valproate should not be prescribed to women younger than 18 years because of the risk of polycystic ovary syndrome and increased risk of unplanned pregnancy in this age group.

- If a woman who is taking valproate is planning a pregnancy, or is pregnant, she should be advised to stop taking the drug. Where appropriate in the treatment of bipolar disorder, an alternative drug (usually an antipsychotic) should be considered.

- If there is no alternative to valproate, doses should be limited to a maximum of 1 gram per day, administered in divided doses and in the slow release form, with 5 mg/day folic acid. However, it is not clear how the serum level of valproate affects the risk of abnormalities.

Side-effects

Please note that the following convention has been used for the classification of side-effects: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1000) and very rare (<1/10,000).

Refer to the SPC for a full list of adverse effects & further information http://www.medicines.org.uk and the current BNF.

This medicine does not have black triangle (▼) status. Serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the MHRA.

Refer patient back to the specialist if any of these side-effects cause concern.

Very Common (> 1%) Nausea, tremor

Common (>1 % and <10%) Liver injury, gastralgia, diarrhoea, headache, extrapyramidal disorder, confusional state, agitation, aggression, hyponatraemia, anaemia, thrombocytopenia, dysmenorrhoea, weight gain, alopecia (transient and/or dose related), memory impairment, nystagmus.

Gastrointestinal disorders (nausea, gastralgia and diarrhoea) frequently occur at the start of treatment and are often transient.

Transient asymptomatic elevations of hepatic enzymes have been seen occasionally, especially in early treatment. Hyperammonaemia rarely reported and severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported.

Referral back to specialist

- there is a poor or partial response to treatment
- the person's functioning declines significantly
- treatment adherence is poor
- the person develops intolerable or medically important side effects from medication
- comorbid alcohol or drug misuse is suspected
- the person is considering stopping any medication after a period of relatively stable mood
- a woman with bipolar disorder is pregnant or planning a pregnancy.
- Any change in mood or development of suicidal thoughts likely to indicate a significant deterioration in the patients condition.
- Development of spontaneous bruising or bleeding.
- Renal and hepatic impairment – refer back for specialist advice – dosage adjustment necessary.
- Breast feeding - refer back for specialist advice

Advice to patient

- Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines.

- Patients must inform the DVLA in the event of a manic episode and they are then advised to cease driving. They should also inform the DVLA about regular medication. It's a duty of the prescriber to ensure the patient is aware of this obligation. A patient whose mental state is stable may however drive safely (with the agreement of the DVLA) on valproate if they are not unduly sedated.

- Gradual discontinuation is generally recommended to avoid the risk of acute withdrawal syndromes or rapid relapse. If contemplating discontinuing at least 4 weeks tapering reducing dosage is recommended. If the patient stops the medication without medical advice please refer to the specialist psychiatrist.

- For female patients of child bearing potential – see under 'Pregnancy' above.

Monitoring

Parameter	Frequency of monitoring			
	Baseline	**At start (1 month)**	**At 6 months**	**Annual review**
Blood pressure	✓			✓
Diet, nutritional status and level of physical activity				✓
ECG	✓			If indicated by history or clinical picture
Fasting blood glucose				✓
Full blood count	✓	✓	✓	✓
Glycosylated haemoglobin				✓
*Lipid Profile	✓			✓
Liver function	✓	✓	✓	✓
Pulse	✓			✓
Fasting blood glucose	✓			✓
Renal function	✓			✓
Thyroid function	✓			✓
Weight or BMI	✓		✓	✓
Smoking status and alcohol use	✓			✓

- Secondary care to do physical health monitoring at baseline and at start of treatment.
- Primary care to do physical health monitoring at 6 months and as part of annual review.
- **Primary care to seek specialist advice from secondary care if results are abnormal**.
- Plasma levels to be done only in exceptional circumstances.
- People with bipolar have higher levels of physical morbidity and mortality than the general population [3].
- Weight gain can also be exacerbated by other drugs such as olanzapine and clozapine [4].

- Additional periodic monitoring where appropriate - Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient. Check FBC and INR before surgery.

Drug Interactions

- **Antiepileptics** – changes to metabolism and enhancement of toxicity reported.
- **Antidepressants, antipsychotics, benzodiazepines, and MAOIs** – enhanced effects of centrally acting drugs. Clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.
- **Aspirin (full dose)** – Shares Phase I metabolism with valproic acid and displaces valproic acid from plasma protein binding sites. Avoid concomitant prescribing except in prophylaxis (75-150mg).
- **Olanzapine** - higher risk of neutropenia, tremor, dry mouth, increased appetite, weight gain, speech disorder & somnolence when prescribed concomitantly.
- **Topiramate** - has been associated with encephalopathy and/or hyperammonaemia.
- **Warfarin** – enhanced anticoagulation

- Weight gain can be exacerbated by other drugs that have this effect (e.g. antipsychotics, particularly clozapine and olanzapine).

Reminder to ask patient about specific problems

- Report any adverse reactions to GP and/or specialist.
- Alert GP/specialist about any change in circumstances which could affect treatment (e.g. pregnancy or drug use).
- Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge and if they have any queries regarding their condition and/or medication

Cost (Drug Tariff Nov 2014)

90 x 250mg tablets £14.60

90 x 500mg tablets £29.15

References

1. Shared Care Protocol for valproate semisodium developed for Bristol, North Somerset & South Gloucestershire. Link to BNSSG shared care page is here
2. Summary of Product Characteristics for valproate semisodium http://www.medicines.org.uk/emc/medicine/25929
3. British National Formulary 68 September 2014 – March 2015
4. NICE CG 185 Bipolar Disorder Sept 2014
5. NICE CG 45 Antenatal and postnatal mental health
6. Maudsley Prescribing Guidelines 11th Edition
7. Drug Tariff November 2014 http://www.ppa.org.uk/edt/November_2014/mindex.htm

Author

1. Bethan Shepherd, Formulary Pharmacist, AWP Mental Health Trust in collaboration with Medicines Optimisation Group (MOG) for AWP, peer review and 3Ts Formulary Working Group.

Date written
October 2014

Date of review
2 years from date of approval (or earlier, if guidance changes)