Valproate for bipolar disorder – formulary status reminder

- Sodium valproate is the OH NHS FT formulary approved valproate preparation.
- Valproic acid is the active moiety that is released from both semi-sodium valproate and sodium valproate.
- Depakote (semi-sodium valproate) should only be prescribed for patients who are currently stabilised on this drug. However, consideration should be given to switching these patients over to sodium valproate where possible. Please note that Depakote is traffic lighted red in Buckinghamshire and will not be prescribed by GPs.
- Depakote 500mg BD is ~3.5x more expensive than an approximately equivalent dose of immediate release sodium valproate (600mg BD) and marginally more expensive than the modified release preparation (1200mg OD). Depakote has to be given in divided doses.
- Modified release sodium valproate is taken once daily and can be prescribed instead of ordinary release preparations when compliance is an issue, to improve tolerability, or to facilitate supervised treatment.
- Dose instructions for using sodium valproate in acute mania are given below.

**Background**
In Dec 2009, the European Medicines Agency completed a review of the safety and effectiveness of valproate in the treatment of manic episodes in bipolar disorder. The Agency’s Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of valproate in this condition outweigh their risks, and that all marketing authorisations for solid formulations (tablets, capsules, granules) containing valproate throughout Europe should be amended to include the treatment of manic episodes in bipolar disorders when lithium is contraindicated or not tolerated. Despite this recommendation only one of the sodium valproate preparations in the UK has altered its licence.

However, the Trust has always endorsed the off-label use of preparations containing valproate (e.g. Epilim which contains sodium valproate) for manic episodes as well as for prevention of further episodes. None of the valproate preparations are licensed for long term prophylaxis in bipolar disorder, although they are often used in this way.

**Dose equivalence**
Valproic acid is the active moiety that is released from both semi-sodium valproate and sodium valproate. Semi-sodium valproate (Depakote) releases marginally more valproic acid per gram than sodium valproate. For example a 500mg Depakote tablet releases 500mg valproic acid, but a 500mg sodium valproate tablet releases 433mg valproic acid¹. Therefore the conversion rate from semi-sodium valproate to sodium valproate is as follows:

1000mg semi-sodium valproate (Depakote) = 1160mg sodium valproate (e.g. Epilim)

If switching between semi-sodium valproate and sodium valproate it may be necessary to round up or down in order to find a dose that is possible with the available tablet strengths (see below):

<table>
<thead>
<tr>
<th>Depakote</th>
<th>Epilim crushable</th>
<th>Epilim enteric coated (e/c)</th>
<th>Epilim Chrono (a prolonged release once daily preparation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250mg, 500mg</td>
<td>100mg</td>
<td>200mg, 500mg</td>
<td>200mg, 300mg, 500mg</td>
</tr>
</tbody>
</table>

**Dose titration for acute mania**
The recommended dose titration for semi-sodium valproate in acute mania is 750mg daily in 2-3 divided doses, increased according to response, usual dose 1-2g daily. Therefore, based on this recommendation, the dose equivalence, and tablet strengths, we suggest the following dosing guidelines for sodium valproate:

**Sodium valproate in acute mania:**
- Initially 800mg daily in 2-3 divided doses (e.g. 400mg BD).
- Increase according to response. Rapid dose titrations are generally well tolerated.
- Usual dose is 20 – 30 mg/kg or a total daily dose between 1000mg to 2000mg.

**Documenting sodium valproate correctly on a T2/T3**
Sodium valproate used to treat bipolar affective disorder should be described on the form as:
“eBNF 4.8.1* Antiepileptic drug oral (one drug) as mood stabiliser used within BNF dose range”.

*NB until we receive further advice about the removal of BNF numbering please use this format

For further advice please contact Medicines Information on 01865 904365 or email: med.info@oxfordhealth.nhs.uk