AWMSG Secretariat Assessment Report – Advice no. 2211
Sodium valproate (Episenta®) prolonged-release capsules (150 mg and 300 mg) and prolonged-release granules (500 mg and 1000 mg)

This assessment report is based on evidence from a limited submission by Beacon Pharmaceuticals Ltd on 1 September 2011.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Sodium valproate (Episenta®) for the 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 sodium valproate for acute mania. The safety and efficacy of Episenta® for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years[1].
Dosing	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 sodium valproate per kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The mean daily dose of sodium valproate usually ranges between 1,000 and 2,000 mg. 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 doses. The company has produced a simplified version of the dosing regime for a patient over 45 kg in body weight. The initial dose is 900 mg of sodium valproate administered once daily at night, increasing to 1200 mg on day two and thereafter increased to the lowest effective dose for the individual patient[2]. Refer to the Summary of Product Characteristics (SPC) for further information[1].
Marketing authorisation date	7 January 2011[3] (licensed for the treatment of all forms of epilepsy on 6 October 2006[1]).

2.0 DECISION CONTEXT

2.1 Background

Bipolar disorder is a chronic psychiatric illness characterised by episodes of depression and elated mood (mania or hypomania)[4]. Manic episodes usually begin abruptly and last for between two weeks and four to five months, whereas episodes of depression tend to last longer (median duration six months). Recovery between episodes may be complete but, although the pattern of remissions and relapses is variable, remissions tend to become shorter as time goes on whilst depressions become more common and

last longer[4]. Figures supplied in the company submission put the point prevalence of bipolar disorder in the UK in 2003 at an estimated 1.3%[5], but a more recent (2009) estimate quoted by the National Institute for Health and Clinical Excellence suggested a point prevalence of up to 5%[6].

The treatment of bipolar disorder frequently includes antimanic agents for the management of current episodes and prevention of future relapses[7]. Lithium salts have historically been the therapy of choice for the treatment of acute episodes of bipolar disorder. However, lithium has a narrow therapeutic window and an unpleasant side-effect profile[5,7,8], and an estimated 40% of patients with bipolar disorder do not respond sufficiently to lithium therapy[8].

Valproate is an anti-epileptic treatment that is available in EU countries in a number of forms, including valproic acid, sodium valproate and valproate semisodium[8], all of which circulate in the plasma as valproate ions[7]. The mechanism of action is not fully understood; valproate is known to increase the activity of the neurotransmitter gamma-amino butyric acid (GABA)[9], but several other mechanisms have also been suggested[10,11].

Following a review of the safety and effectiveness of valproate in the treatment of manic episodes in bipolar disorder in August 2010, the European Medicines Agency (EMA) concluded that all marketing authorisations for medicines containing valproate throughout Europe should be amended to include the treatment of manic episodes in bipolar disorders when lithium is contraindicated or not tolerated[8,9]. On 7 January 2011, sodium valproate (Episenta®) received a licence extension for the treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated[1,3].

2.2 Comparators

The comparator requested by the Welsh Medicines Partnership (WMP) was valproate semisodium (Depakote®).

2.3 Guidance and related advice

- British Association for Psychopharmacology (BAP). Evidence-based guidelines for treating bipolar disorder (2009)[12].
- National Institute for Health and Clinical Excellence (NICE). Clinical Guideline 38. Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary (2006)[4].
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN publication number 30. Bipolar affective disorder. A national clinical guideline (2005)[13].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission focuses on demonstrating clinical equivalence of sodium valproate and valproate semisodium. Evidence presented includes an indirect comparison of sodium valproate and valproate semisodium[3], and an evaluation of valproate-containing products for the treatment of bipolar disorder conducted by the Committee for Medicinal Products for Human Use (CHMP)[8].

Several studies have previously demonstrated that sodium valproate and other valproate formulations, including valproate semisodium, are safe and effective in the treatment of manic episodes in bipolar disorder[7,14–18].

3.1 CHMP review of valproate for the treatment of manic episodes in patients with bipolar disorder

The CHMP review of the efficacy of valproate in the treatment of bipolar disorder was based on evidence from sixteen randomised, comparative double-blind or open-label clinical trials and included 2,500 patients, of whom over 1,400 received valproate[8].

It concluded that valproate is efficacious in the acute treatment of manic episodes over 21 days. However, the evidence of efficacy of valproate in the prevention of mood episodes and for maintenance of treatment effects over 12 weeks were both considered incomplete[8].

Additionally, the various forms of oral valproic acid/valproate were concluded to differ in their rate of absorption but bioavailability was found to be comparable for practically all formulations[19]. CHMP concluded that the available evidence suggested that the efficacy of valproate in bipolar disorder, at least in the treatment of acute mania, does not depend on the pharmaceutical form used[19].

3.2 Indirect comparison of sodium valproate and valproate semisodium

The company submission includes an indirect comparison of valproate semisodium and sodium valproate[3], which states that both formulations have demonstrated effectiveness in the treatment of mania[10,15–17]. It is concluded that the evidence does not support the idea that valproate semisodium is better tolerated or more effective in the treatment of manic episodes in patients with bipolar disorder than sodium valproate. However, the authors of the comparison acknowledge that there is no trial that directly compares the two formulations[10].

3.3 Safety

The safety profile of valproate is well characterised from forty years in the treatment of epilepsy[8]. During an evaluation of the safety of valproate for the treatment of patients with bipolar disorder, CHMP concluded that it was well tolerated and highlighted no unexpected safety concerns[8]. The major safety concerns of valproate treatment highlighted by CHMP relate to liver dysfunction and pancreatitis, while nausea, sedation and extrapyramidal disorders were added to the SPC[8].

CHMP concluded that all valproate formulations appear to be acceptably tolerated and found no difference in either the frequency or nature of adverse reactions between sodium valproate and valproate semisodium[19]. A comparison of the safety profiles of valproate semisodium and sodium valproate, included as part of the company submission, also concluded that there is no evidence to support the idea that valproate semisodium is better tolerated than sodium valproate[10].

3.4 WMP critique

- As requested by WMP, the company submission uses Depakote® as the comparator[3]. However, a direct comparison of the safety and effectiveness of Depakote® and Episenta® for the treatment of manic episodes in bipolar disorder has not been provided. An indirect comparison has been included[3], which concludes that there is no evidence to substantiate a difference between the two therapies[10]. Additionally, a review of the safety and effectiveness of valproate in the treatment of manic episodes in bipolar disorder has been provided, which suggests that valproate formulations are comparable in terms of bioavailability, effectiveness and tolerability, regardless of the pharmaceutical form[8].
- The Episenta® SPC states that “when changing from sodium valproate enteric coated tablets to Episenta® it is recommended to keep the same daily dose”[1].

- Episenta® treatment administration can be given once or twice daily[1], while valproate semisodium Depakote® is administered in two or three daily doses[15].
- Adherence to prescribed medication is frequently poor in bipolar disorder: a 2007 study found that only 54.1% of patients with bipolar disorder were fully adherent to treatment regimen[20]. The company submission suggests that the reduced administration frequency of Episenta® could result in increased adherence over Depakote®[3]. Furthermore, recent guidelines suggest that switching to once daily treatment administration should be considered in order to reduce side effects and increase adherence[12].
- CHMP has suggested that slow-release formulations could be advantageous for compliance reasons and for avoiding high plasma peaks which can be associated with frequent adverse events[8].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

The limited submission provided by the company does not include any evidence on the cost-effectiveness of sodium valproate (Episenta®) prolonged release capsules or granules for the treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated[3]. Cost-effectiveness evidence is not required for a limited submission.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and Methods

The company has assumed a prevalence of bipolar disorder in the general adult population of 1.3%, from which it estimates there are 39,000 patients with bipolar disorder in Wales[3]. The company assumes that 40% (15,600) of these patients are treated with Depakote®, (no further details provided) and an unknown percentage with lithium. Assuming a maximum dose of 2000 mg per patient per day, the company estimates that the annual cost of treatment of bipolar patients with Depakote® would be around £6,147,024 per year, compared with £4,669,080 if all such patients were to be treated with Episenta®, i.e. an annual saving of £1,477,944.

5.1.2 WMP critique of the company's budget impact estimates

There is some uncertainty in the company's estimates of bipolar disorder prevalence in adults in Wales. The company assumes that 40% of all bipolar patients are receiving Depakote® for continued treatment during and after a manic episode, although no basis for this assumption is provided[3]. The cost savings reported by the company reflect a scenario of 100% of patients taking Depakote® being treated with Episenta® instead, which is unlikely in practice. The absolute cost savings reported by the company are therefore unlikely to be realised in practice. Nevertheless, the acquisition costs of Episenta® are lower than those for Depakote® (See Table 1, Section 5.2), and its use in place of Depakote® would be cost saving based on current list prices.

5.2 Comparative unit costs

Table 1 shows example annual drug costs for the ongoing treatment during and after manic episode in bipolar disorder when lithium is contraindicated or not tolerated.

Table 1. Example acquisition costs.

Drug	Regimen	Annual cost per patient
Episenta® (sodium valproate) 150 mg and 300 mg capsules	1000–2000 mg once daily	£142.35 (900 mg per day) – £332.15 (2,100 mg per day)
Episenta® (sodium valproate) 500mg and 1,000mg granules	1000–2000 mg once daily	£149.65 – £299.30
Depakote® (valproate semisodium) 250 mg and 500 mg tablets	1000–2000 mg per day	£197.02 – £394.04
Costs are based on BNF list prices[21]. *See SPCs for full dosing details.* *This table does not imply therapeutic equivalence of drugs or the stated doses.*		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

WMP is of the opinion that sodium valproate (Episenta®) may be suitable for shared care within NHS Wales.

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