European Medicines Agency

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ASSESSMENT REPORT

Valproic acid/Valproate containing medicinal products

PROCEDURE No: EMEA/H/A-31/1163

Referral under Article 31 of Directive 2001/83/EC, as amended

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1 BACKGROUND INFORMATION ON THE PROCEDURE

On 16 April 2009, Medicines Evaluation Board (MEB) in The Netherlands triggered a referral under Article 31 of Directive 2001/83/EC, as amended (see appendix 1). The CHMP was requested to give its opinion on whether the marketing authorisations for valproate containing medicinal products should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Bipolar disorder is a severe mental disorder characterized by recurrent episodes of mania and depression, which as a recurrent affective illness produces significant distress and dysfunction, ranking among the top 30 causes of worldwide disability.

In the DSM IV classification of psychiatric diseases a distinction is made of four clinical forms: bipolar I disorder, bipolar II disorder, cyclothymic disorder and bipolar disorder NOS. The two most frequent forms are:

- Bipolar I disorder - alternating episodes of major depression and classic mania, with at least one manic or mixed episode.
- Bipolar II disorder - alternating episodes of major depression with hypomania, with at least one Major depressive episode and at least one hypomanic episode.

The majority of patients with bipolar I disorder present both depressive and manic episodes, while about 10%-20% manifest only manic episodes. Mixed episodes, during which patients simultaneously manifest symptoms of both mania and depression, are not exceptional, with approximately 40% of patients experiencing a mixed episode at one time or another. It has been estimated that around 60% of patients with a first manic episode will experience a new mood episode within four years. However, in some patients, referred to as “rapid cyclers”, mood episodes alternate much more frequently and these patients are particularly difficult to treat. The worldwide lifetime prevalence of bipolar I disorder is about 0.4% to 1.6% and of bipolar II disorder about 0.5% and is similar in both genders. The onset of the disease is mostly during adolescence or early adulthood and the most patients have a long-lasting disorder. Bipolar disorder is associated with significant psychiatric co-morbidity, high levels of substance abuse, and a high risk of suicide. 25%-50% of the patients attempt suicide at least once and about 10% - 20% commit suicide. Therefore the increased morbidity and mortality rate among this patient population is associated with important social and economic burden.

The treatment of bipolar disorder includes management of the current mood episode and prevention of recurrence of next mood episodes. Although the pathogenesis of bipolar disorder is unclear, it is known that mood stabilizers, such as valproate, can prevent its recurrence.

Furthermore, lithium is widely used as first-line treatment for acute mania, because of its confirmed efficacy as a mood stabilizer. Other therapeutic options for bipolar disorder are neuroleptics, benzodiazepines, and valproate.

Among the mood stabilizers lithium has the longest track record and is therefore a reasonable first choice. However, it has recently been estimated that up to 40% of the patients with bipolar disorder do not or insufficiently respond to an adequate lithium therapy. In addition there is a considerable risk due to the narrow therapeutic window of this substance. Anticonvulsants are increasingly becoming an alternative.

Valproate is a well-known anti-epileptic substance. In most of the EU Member States valproate is also approved for the treatment of patients with bipolar disorder (approved in 25 European countries, in 21 countries with a first-line indication).

Concerns were raised by the Netherlands regarding the efficacious and safe use of valproate containing medicinal products in the acute treatment of manic episodes and the prevention of recurrence of mood episodes in patients with bipolar disorder. It was highlighted that although the indication exists in many Member States, sustained efficacy both in acute mania as well as in the prevention of recurrence of mood episodes has not been clearly demonstrated in well designed clinical trials which comply with the requirements of the CPMP Note for Guidance on Clinical Investigation of Medicinal products for the Treatment and Prevention of Bipolar Disorder (CPMP/EWP/567/98).

2.2 Clinical Efficacy

To support the bipolar indication the MAHs submitted several published studies.
The evidence of the efficacy of valproate in the treatment of bipolar disorder comes from sixteen randomised, comparative double-blind or open-label clinical trials:

- eight evaluating valproate monotherapy in acute mania (three or twelve week studies)
- five evaluating valproate combination therapy in acute mania
- three evaluating valproate for prevention of recurrence of mood episodes in bipolar disorder (twelve to twenty months)

These studies included nearly 2,500 patients, of who over 1,400 received valproate. As such, this represents one of the largest bodies of clinical trial data relating to the pharmacotherapy of bipolar disorder. In addition, valproate has been used as the reference comparator treatment in many Phase III studies of atypical antipsychotic drugs in the treatment and prevention of mania.

2.2.1. Treatment of acute mania

The main clinical studies presented by the MAHs for the use of valproate in acute mania are summarised in the Table 1 below and are discussed later.

Table 1: Clinical studies of valproate in acute mania

No	Study	Design	Treatment arms	# Patients	Duration
Pivotal studies of valproate monotherapy in acute mania					
1	**Pope et al., 1991**	Double-blind	Placebo VPA 750 mg/d	43	21 days
2	**Bowden et al., 2006**	Double-blind	Placebo VPA 25 mg/kg/d	377	21 days
3	**Bowden et al., 1994**	Double-blind	Placebo VPA 750 mg/d Li 900 mg/d	179	21 days
4	**NEW DELI**	Open-label	VPA 20 mg /kg/d Li 400 mg/d	300	3 months
5	**VALID**	Open-label	VPA 20 mg /kg/d Li 600 mg/d	257	3 months
6	**Zajecka et al., 2002**	Double-blind	VPA 20 mg /kg/d OLZ 10 mg/d	120	3 months
7	**Tohen et al., 2002**	Double-blind	VPA 750 mg/d OLZ 15 mg/d	251	21 days
Pivotal studies of valproate combination therapy in acute mania					
8	**Müller-Oerlinghausen et al., 2000**	Double-blind	AΨ + Pbo AΨ + VPA 20 mg/kg	136	21 days
Supportive studies of valproate monotherapy in acute mania					
9	**Freeman et al., 1992**	Double-blind	VPA 1500 mg/d Li 0.5 meq/kg/d	27	21 days
Supportive studies of valproate combination therapy in acute mania					
10	**Yatham et al., 2004**	Open-label	Li + RIS 0.5-2 mg VPA +RIS 0.5-2 mg	79	12 weeks
11	**Vieta et al., 2008**	Double-blind	VPA + Pbo VPA + ARI 15 mg/d	384	6 weeks
12	**Bahk et al., 2005**	Open-label	RIS 0.5-2 mg + TPA 50 mg RIS 0.5-2 mg +VPA 750 mg	74	6 weeks
13	**Maina et al., 2007**	Open-label	Li + VPA 0.5-1.5 mg Li + OLZ 7.5-15 mg	21	8 weeks

ARI: aripiprazole; AΨ: antipsychotic; Li: lithium; Pbo: placebo. OLZ: olanzapine; RIS: risperidone; VPA: valproate; TPA: topiramate.

The efficacy of valproate for the treatment of acute mania has mainly been demonstrated in two, large, randomised placebo-controlled trials (Bowden et al., 2006; Bowden et al., 1994):

Bowden *et al.* (1994) used an active comparator (lithium), as required by the current European guideline NfG on clinical investigation of medical products for the treatment and prevention of bipolar disorder (CPMP/EWP/567/98). The treatment duration was 21 days. Concerning the primary efficacy variable (change in the Manic Rating Scale (MRS), at least 50% improvement occurred in 48% and 49% of the valproate semisodium and lithium groups, respectively and in only 25% of the placebo group. The rates of improvement in the two groups were significantly greater than the improvement observed in the placebo group (p=0.004 and p=0.025, respectively). The effect sizes for the lithium-treated group were comparable to those for the valproate semisodium group. However, due to the smaller size of the lithium group (N=36) compared to the valproate semisodium group (N=69) and placebo group (N=74), respectively, most comparisons of lithium and placebo did not reach statistical significance. Overall, efficacy of valproate in the treatment of acute mania for 21 days has been demonstrated in this study.
Due to the study results the application of valproate in the treatment of acute mania was approved by the FDA.

Bowden *et al.* (2006) conducted a randomised, placebo-controlled multicenter study. Extended release valproate was confirmed to be safe and efficacious in the treatment of an acute manic episode associated with bipolar disorder. Compared with placebo (N=185), improvement in the primary response variable (i.e. the Mania Rating Scale, MRS) was significantly better in the valproate group (N=192), starting on day 5 of treatment and for all subsequent assessments up to day 21. No worsening of depressive symptoms was observed. However, the maintenance of effect is not presented after 21 day and no active comparator was used.

Bowden *et al.* (2008): A subsequent open, but randomised study was performed by the same working group in order to demonstrate that the anti-manic efficacy of valproate can be maintained over 12 weeks of treatment. As based on remission rates, lithium and valproate showed comparable efficacy (65.5% vs 72.3%). However, this study has an open-label design.

Pope *et al.* (1991): A randomised, placebo-controlled, double-blind study on the use of valproate in 36 patients with acute manic episode who had previously failed to respond to or tolerate lithium. The treatment duration was 7-21 days. Lorazepam up to 4 mg/day during the first 10 days of treatment was permitted. Valproate proved significantly superior to placebo according to all three psychiatric rating scales used in this study. However, the patient number was limited and patients used lorazepam the first 10 days of the study as co-medication.

NEW DELI (2006): A randomised, open-label, parallel-group study where valproate was compared to lithium over 12 weeks as acute and continuation therapy. The study randomised 300 patients presenting with an acute manic episode to treatment with lithium or valproate. The authors concluded that valproate represents an effective alternative to lithium for continuation therapy of acute mania. However, the study has an open-label design and the placebo arm is missing.

VALID (2007): A randomised, open-label, parallel-group, two-arm study comparing valproate with lithium in 257 patients. The study demonstrated the equivalence of valproate and lithium in improving manic symptoms, as measured with the YMRS, in patients with bipolar type I disorder. However, this study is also just an open-label study without placebo arm.

Zajecka *et al.* (2002): A randomised, 12-week, double-blind, parallel-group, multicenter clinical study in 120 patients with type I bipolar disorder hospitalised for acute mania in order to compare valproate with olanzapine. No significant difference in efficacy was found between treatment groups, but valproate had a more favourable safety profile (e.g. weight gain). However, the study lacks the placebo arm.

Tohen *et al*. (2002): A randomised, double blind, parallel-group, two-arm, 21-day study comparing valproate with olanzapine. The authors concluded that the olanzapine group had significantly greater efficacy on mania as charaterised by the YMRS score. Significantly more weight gain and cases of dry mouth, increased appetite and somnolence were reported with olanzapine, while more cases of nausea were reported with valproate. However, the study duration was only 21 days and the placebo arm is missing.

Müller-Oerlinghausen *et al.* (2000): A randomised, multicenter, double-blind, 21-day placebo-controlled study, where the efficacy of valproate in add-on therapy was compared to antipsychotic monotherapy (+ add-on placebo) showed that the combined treatment with valproate achieved a faster and greater improvement in YMRS scores.

From the various studies discussed above a certain degree of evidence has been determined for efficacy of valproate in acute mania, although all these studies suffer from several shortcomings.

The positive assessment is also shared by a recent Cochrane review of Macritchie *et al.* (2009), confirming that *"... there is consistent, if numerically limited, evidence from randomised trials that valproate is an efficacious treatment for acute mania. The relative efficacy of valproate compared to lithium and carbamazepin is unclear. Valproate may be less effective than olanzapine in reducing manic symptoms, but cause more sedation and weight gain.*"

2.2.2. Prevention of recurrence of mood episodes

Table 2: Clinical studies of valproate in prevention of recurrence of mood disorders

Randomised, controlled studies of valproate in the prevention of mood episodes				
Study	**Design**	**Treatment arms**	**Patients**	**Duration**
Bowden *et al.*, 2000	Double-blind, stabilised patients	Placebo Valproate Lithium	382	52 weeks
Calabrese *et al.*, 2005	Double-blind, stabilised	Valproate Lithium	60	20 months
Tohen *et al.*, 2003	Double-blind, Non-stabpatients	Valproate Olanzapine	180	47 weeks
Revicki *et al.*, 2005	Open-label Non-stab. patients	Valproate Lithium	201	52 weeks

Two pivotal studies have been performed with valproate in the indication recurrence of mood episodes in patients with bipolar disorder:

Bowden *et al*. (2000) published a large randomised, double-blind, parallel-group multicenter study on treatment outcomes over a maintenance period of 52 weeks. Patients who met the recovery criteria within 3 months of the onset of an index manic episode (n=372) were randomised to prophylactic treatment with valproate, lithium, or placebo in a 2:1:1 ratio. Although the treatments during maintenance therapy did not differ significantly on time to recurrence of any mood episode (depression, mania), which was the defined primary outcome measure, patients treated with valproate had better outcomes on several secondary outcome measures than those treated with lithium or placebo. After 12 months of treatment following a manic index episode, 41% of patients treated with valproate were still in remission compared to 24% of patients treated with lithium and 13% of patients treated with placebo. Valproate was superior to lithium in longer duration of successful prophylaxis, less deterioration in Global Assessment Scale scores and depressive symptoms. As a consequence of the low rates of development of mania and depression in the placebo arm, the study had insufficient power to detect significant differences between groups by survival analyses and cannot be seen as a negative study for valproate, but as failed study.

In **2005, Calabrese *et al.*** completed a randomised, 20-month, double-blind, parallel-group trial comparing valproate and lithium in 60 patients suffering from rapid cycling bipolar disorder. Patients from the valproate group performed better in several efficacy parameters, but none of the differences reached statistical significance. However, significantly more patients in the lithium group experienced various adverse effects (tremor, polyuria, polydipsia). The two-arm study in rapid cyclers could be criticised for its low statistical power, which could be an unanticipated consequence of the high drop-out rate in the stabilisation phase of the study. Furthermore a placebo arm is missing.

However, both studies fulfil the requirements set out in the current Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder (CPMP/EWP/567/98). Both were randomised, double-blind, controlled studies with an appropriate comparator. One study included a placebo group and both used lithium as an active comparator. In both studies, serum levels of both lithium and valproate were monitored and doses adjusted to ensure

that adequate doses were administered. The treatment period of twelve months was sufficient to evaluate efficacy. Both studies included one of the two clinical endpoints recommended in the current CPMP guideline (CPMP/EWP/567/98), namely time to recurrence or rates of recurrence, as the primary outcome measure.

Tohen *et al.* (2003). This study represented a double-blind continuation of the acute mania study comparing valproate and olanzapine discussed earlier (Tohen *et al,* 2002). The total treatment duration from randomisation was 47 weeks. During the long-term prophylactic phase, patients remained in their original randomisation group. The authors concluded that symptomatic remission occurred sooner and overall mania improvement was greater for olanzapine than for valproate, but rates of bipolar relapse did not differ.

Revicki *et al.* (2005): A randomised, naturalistic, 1-year, comparative study of lithium and valproate in patient with bipolar I disorder. It was concluded by the authors that clinical and Quality of Life outcomes for valproate and lithium were comparable using for the recurrence prevention treatment of bipolar disorder.

***Post-hoc* analyses**

As the large, placebo- and active-controlled study, published by Bowden *et al.(* 2000) failed to show statistical significant difference in the primary outcome measure several *post-hoc* analyses have been performed:

Cochrane analysis: The endpoint – proportion of patients discontinuing the study due to a mood disorder – being originally a secondary outcome, was selected as primary outcome for this analysis because of the high clinically relevance. Thus, patients treated with valproate left the study significantly less frequently due to the occurrence of a mood episode than patients treated with placebo. Additionally, there was no significant difference in the patient numbers in the valproate group who left the study due to occurrence of a mood episode comparing with patients numbers in the lithium group.

McElroy *et al.* (2007): Investigation of the outcome in the subgroup of patients who had responded to the acute anti-manic treatment with valproate and who continued valproate during the double-blind recurrence prevention phase. Patients treated with valproate during open label part and later randomised to valproate in double blind long-term part had a significant longer period before development of any mood episode compared to those randomised to either placebo or lithium.

Gyulai *et al.* (2003): This post-analysis was performed to analyse depressive morbidity specifically. It was observed that a significantly lower percentage of patients in the valproate group discontinued early for depression than in the placebo group; a trend towards a longer time to first depressive episode in the valproate group compared to the lithium group was also observed.

Though *post-hoc* analyses provide naturally less robust results, some significant differences in favour of valproate in recurrence prevention could be shown.

Bipolar depression

Concerning bipolar depression, one small placebo-controlled study over 8 weeks indicated improved control of depressive symptoms with valproate (Davis *et al.,* 2005). However, there is no sufficient evidence of efficacy of valproate in acute bipolar depression (see also recommendations by aforementioned treatment guidelines).

In the *post-hoc* analysis of the Bowden study published in the year 2000 (Gyulai *et al.,* 2003), discontinuation due to depression (which was a secondary outcome parameter in the original analysis)

occurred significantly less frequent in valproate treated patients compared to placebo patients. A trend towards better outcome compared to lithium was also observed in this study.
In the study published by Calabrese *et al*., 2005, relapse rates into a depressive episode were 29% for valproate versus 34% for lithium.

2.2.3. Chemical forms and formulations of valproate:

The various forms of oral valproic acid/valproate differ in their rate of absorption but bioavailability is comparable for practically all formulations. Modified-release formulations present flattened plasma concentration peaks and allow sustained steady-state plasma levels to be achieved with once daily dosing.

The relationship between therapeutic response and the pharmaceutical form of valproate administered has not been evaluated systematically. The majority of the studies of valproic acid/valproate in the treatment of acute mania and all of those for recurrence prevention in bipolar disorder have been performed with valproate semisodium.

Very similar results were generated by two studies in acute mania performed in the USA using very similar protocols to compare valproate semisodium enteric-coated (gastro-resistant) tablets with placebo (Bowden *et al*., 1994) and valproate semisodium prolonged release formulation with placebo.

Additionally, two European studies using two different modified release formulations of valproate (Chrono and Chronosphere) (Sanofi-Aventis, 2007; Bowden *et al.,* 2008) both demonstrated non-inferiority to lithium, whilst a US study comparing valproate semisodium and lithium to placebo demonstrated similar effect sizes for both drugs.

Based on the submitted data it cannot be concluded, that efficacy of valproate in the claimed indication is dependent on chemical form or formulation. The available evidence suggests that the efficacy of valproate in bipolar disorder, at least in the treatment of acute mania, does not depend on the pharmaceutical form used. All formulations appear to be acceptably tolerated, with no difference in either the frequency or nature of adverse reactions between sodium valproate, semisodium valproate or valpromide having been observed. Furthermore, according to clinical practice and the dose recommendations, the daily dose should be adapted individually to the clinical response between a specific dose range and the lowest effective dose should be used in the prevention of recurrence in bipolar disorder. However, for theoretical reasons slow-release formulations could be advantageous for compliance reasons and also for avoiding high plasma peaks which may be accompanied by frequent adverse effects.

2.2.4. Dose administration

The relationship between therapeutic response and the dose of valproate administered has not been evaluated systematically. In many studies, the initial defined dose (in most cases close to 20 mg/kg) was adjusted either according to clinical judgment or according to serum valproate concentrations in order to achieve a target serum concentration range, which varied between studies. In most of the studies performed, the mean final dose was around 1,500 mg/day. The most recent studies, including all those performed in Europe, have used an initial dose of 20 mg/kg/day rather than slow titration upwards from 750 mg/day (as was the case in the earlier studies). These studies show that such a treatment regimen allows effective and rapid control of manic symptoms.

Several studies have examined the relationship between valproic acid concentrations and clinical improvement in patients with acute mania. A number of these have suggested that response is related to blood levels or to the rise in blood levels and there is consistent evidence that the threshold of responsiveness and anti-manic efficacy is around 50µg/ml.

Furthermore, no dedicated studies have evaluated the relationship between safety and administered dose in patients with bipolar disorder treated with valproate. Nonetheless, studies in epilepsy suggest that several of the more frequent adverse effects of valproate appear to be dose-related; these include tremor, gastrointestinal effects, weight gain, alopecia, drowsiness and elevation of hepatic enzymes. In bipolar disorder, the final dose achieved in the studies (around 1500mg/day) appears to be acceptably tolerated, with relatively few patients discontinuing treatment due to the occurrence of adverse events. With respect to the choice of initial dose of valproate, it is difficult, given the limited data available, to draw firm conclusions on the relative tolerability of a 20 mg/kg/day initial dose regimen compared to a slow titration regimen. Nonetheless, the use of a high initial dose appears to be associated with a comparable incidence of adverse events to that seen with a slow titration regimen. The adverse event profile is different to that of lithium, but the overall tolerability of valproate 20 mg/kg/day is no worse than that of the latter drug. On the other hand, the tolerability of this valproate treatment regimen appears to be superior to that of olanzapine in terms of weight gain. No specific safety issue has been identified for the 20 mg/kg/day regimen.

In conclusion, the dose-effect relationship has not been explored systematically to identify the optimal dose of valproate to use in the treatment of bipolar disorder, although there is evidence for a relationship between serum levels and efficacy. From a clinical point of view, the target dose should be the lowest dose that allows effective control of manic symptoms. Rapid titration up from an initial dose of 20 mg/kg/day seems to be effective and well-tolerated. For the prevention of recurrence, continuation of the dose that allowed satisfactory control of manic symptoms during the acute phase appears appropriate.

2.2.5. Other Studies submitted by MAHs

The additional literature presented by the generic MAHs did not contribute to the knowledge necessary for making a benefit/risk balance. This is because the quoted studies are not conforming to the clinical investigational guidelines for bipolar disorder.

2.2.6 Discussion and conclusion on Efficacy

Acute mania

Based on the literature references provided it can be concluded that there is evidence for the efficacy of valproate in the acute treatment of manic episode, which has been demonstrated in placebo controlled studies of three weeks. There is also some evidence for maintenance of effect in treatment of acute mania episode (up to 12 weeks), although the 12 weeks studies lack a placebo arm, which is a deficiency.

Prevention of Recurrence

Concerning recurrence prevention of mood episodes, evidence of efficacy of valproate is mainly based on two double-blind studies with a maintenance period of 52 weeks and 20 months duration, respectively (Bowden *et al.,* 2000 and Calabrese *et al*, 2005). Whereas the Bowden study which was lithium- and placebo- controlled failed to show a statistically significant difference with respect to the primary outcome criterium (time to recurrence of any mood episode), patients treated with valproate had better outcomes on several secondary outcome measures than those treated with lithium or placebo. After 12 months of treatment following a manic index episode, 41% of patients treated with valproate were still in remission compared to 24% of patients in the lithium group and 13% of patients in the placebo group.

Though *post-hoc* analyses are generally of less value with respect to robustness of data, the performed post-hoc analyses of the large Bowden study (Cochrane group, McElroy *et al.* (2007), Gyulai *et al.* (2003) revealed some results which are considered remarkable: Whereas, in the original

analysis time to recurrence of any mood episode or depressive episode, respectively was not significantly different in the three treatment groups, post-hoc analyses showed that valproate treated patients dropped out significantly less frequent than placebo treated patients because of a mood episode and due to a depressive episode, respectively, whereas the respective difference was not statistically significant compared to lithium treated patients (Cochrane group, Gyulai, 2003).

Furthermore, it was found, that in the subgroup of patients treated with valproate during the open-label phase, patients who were randomized to valproate during maintenance phase had a significantly longer period before development of any mood episode compared to those randomized to either placebo or lithium (McElroy, 2007).

In the two-arm study performed by Calabrese and co-workers (2005) patients in the valproate group performed better in several efficacy parameters compared to the lithium group (in a statistically non-significant way), however significantly more patients in the lithium group experienced various adverse effects (tremor, polyuria, polydipsia) compared to the valproate group. It could be criticised that the latter study was not placebo-controlled, however the use of lithium in bipolar disorder, especially in the recurrence prevention is the established standard of care.

Recurrence prevention of both mania and depression has not been demonstrated. The two recurrence prevention studies are of sufficient duration and have an active comparator as requested by European guidelines. However one study is lacking a short placebo arm, which is a deficiency and brings doubts about the validity of the results. In addition the time to recurrence of manic and depression events has not shown differences. Evidence of efficacy of valproate in the prevention of mood episodes is thus not completely convincing based on the performed clinical studies alone.

2.3 Clinical Safety

The available studies on the use of valproate to treat patients with bipolar disorder have shown that the drug was generally well tolerated and revealed no unexpected safety concern. The safety profile of valproate is well characterised from forty years of experience in the treatment of epilepsy. The major potentially serious safety concerns relate to liver dysfunction and pancreatitis. Fatal hepatotoxicity is rare, idiosyncratic and not apparently dose-related. No unexpected signals have been identified from post-marketing surveillance. A specific issue for the safety of drugs used for the treatment of bipolar disorder is potential interactions with other psychotropic drugs frequently used in these patients, notably antipsychotic and antidepressant drugs. Dedicated studies have shown that valproate can be used safely in combination with antipsychotic drugs. Moreover, no specific safety issues have been identified in studies in which antidepressant co-medication has been used in patients with bipolar disease.

Adverse Events

Since valproate is proposed as another mood stabilizer in the treatment of bipolar disorder, most comparisons are made with lithium. The safety profiles of valproate and lithium are not consistently different; however there were more severe AEs and discontinuations in the lithium arms, indicating that for some patients, valproate could be a better treatment option.

Another treatment option in bipolar disorder is atypical antipsychotics. In monotherapy valproate seems to have a more favourable safety profile as compared to olanzapine. Olanzapine induced more AEs like weight gain, somnolence and metabolic changes in long term application. Valproate is associated more frequently with “nausea” and “sedation”.

A significant proportion of bipolar patients do not respond adequately to one medication and therefore combination therapy is often applied. A general impression from the presented clinical studies is that valproate can be used in combination with antipsychotics without causing considerable additional safety issues. In some cases the combination of antipsychotic and lithium induced more adverse events.

The following citations in Martindale (thirty-sixth edition 2009) underlay the inclusion of extrapyramidal disorders in the SPC in section 4.8: *"Very rare cases of extrapyramidal symptoms or reversible dementia associated with cerebral atrophy have been reported."* and *" An extrapyramidal syndrome of tremor and rigidity, unresponsive to benzatropine or trihexyphenidyl, developed in a 52-year-old man with schizophrenia given a therapeutic trial of sodium valproate 1 to 2 g daily"* (Lautin *et al.,* 1979). "Giving sodium valproate to a man with dystonic movements of the neck and spine produced a severe subjective and objective deterioration in his symptoms, which returned to their previous severity on withdrawal of the drug" (Dick *et al.,* 1980).
As conclusion, the possible ADRs "nausea", "sedation" and "extrapyramidal disorders" should be listed in the SPC, section 4.8.

Formulation

With respect to the formulation, there is some evidence that gastro-resistant tablets might provide some advantages in terms of safety as compared to immediate release formulation.

Pregnancy

A teratogenic risk associated with the use of valproate in pregnant women, including the potential for delayed intellectual development has been identified following *in utero* exposure to valproate. Therefore, in women envisaging a pregnancy, valproate should not be used for the treatment of manic episodes, unless safer alternatives prove to be ineffective or are not tolerated. Women of child-bearing potential have to use effective contraception.

Suicidality

In 2008, in light of the results of the US FDA meta-analysis of clinical trial data for antiepileptics, and in light of the spontaneous and literature reports, the PhVWP concluded that any antiepileptic drug may be associated with a low risk of suicidal thoughts and behaviour.

This meta-analysis of 199 placebo-controlled trials on 11 antiepileptic drugs, including valproate, used for epilepsy, psychiatric disorders or other indications, was carried out to evaluate the potential for elevated risk of suicidality. These trials consisted of 27,863 patients in drug arms and 16,029 patients in placebo arms. Among the 2,319 patients enrolled in the valproate studies, 992 were in the placebo arm and 1,327 were in the treatment arm: 1,285 for psychiatric indications, 147 for epilepsy, and 887 for other indications. Among the 10 drugs with any events, the estimated odds ratios (ORs) for suicidal behaviour or ideation were less than 1 (favouring treatment) for 2 drugs, i.e., valproate and carbamazepine; the estimated OR and 95% confidence interval for valproate was 0.72 (0.29-1.84). The ORs were greater than 1 for the other 8 drugs.

On the basis of the evidence available to the PhVWP, it was not possible to establish whether the risk of suicidal thoughts and behaviour differed between antiepileptic drugs. Furthermore, the mechanism by which antiepileptic drugs may increase the risk of a patient having suicidal thoughts and behaviour was not known and therefore it was not possible to identify which drugs might not be associated with increased risk.

The PhVWP agreed that SPCs for all antiepileptics across the European Union should be modified with regard to suicidality with the addition of a warning

Discussion on Safety

Following the literature presented as well the post-marketing experience the adverse events of "nausea", "sedation" and "extrapyramidal disorders" are proposed to be added to the Section 4.8 "Undesirable effects" of the SPC.

Pregnancy

A teratogenic risk associated with the use of valproate in pregnant women Therefore, in women envisaging a pregnancy, valproate should not be used for the treatment of manic episodes, unless safer alternatives prove to be ineffective or are not tolerated. Women of child-bearing potential have to use effective contraception.

Suicidality

The PhVWP agreed in 2008 that SPCs for all antiepileptics across the European Union should be modified with regard to suicidality with the addition of a warning. This is also recommended for any of the valproate products that do not include the warning at present.

In general, it can be concluded that there is limited safety information, particularly on the long term use of valproic acid/valproate in bipolar disorder patients.

2.4 Risk Management Plan

The need for a Risk Management Plan was discussed with the MAHs. Taking into account that in different EU member States the authorised valproate products may have or not the indication for the bipolar disorder the CHMP agreed with the following:

The MAHs for valproate authorised products applying to the new indication should submit a Risk Management Plan to the national competent authorities (NCAs) of the respective member states. The content, objectives and implementation of the RMP should be discussed between the relevant MAH and the NCA.

2.5 Overall Benefit Risk Assessment

The conducted studies demonstrate efficacy of valproate in the treatment of acute mania over 21 days, but evidence for the maintenance of the treatment effect up to 12 weeks of treatment is not considered complete. Due to the insufficient data presented for efficacy in recurrence prevention a positive recommendation for the recurrence prevention cannot be granted.

According to the CHMP recommendation for valproate containing medicinal products the indication should be adapted as following due to the limitations and shortcomings of the data from clinical trials:

> "*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 for acute mania*."

Basically, there is a positive benefit-risk relation with regard to the aforementioned indication.

2.6 Re-examination procedure

Various MAHs submitted written notice to the European Medicines Agency by 27 February 2010 to request a re-examination of the Opinion. The detailed grounds for the re-examination request were submitted to the Agency by 13 April 2010.

The grounds for re-examination relate mainly to implementation issues rather than to scientific grounds. All MAHs expressed their agreement with the overall recommended amendments to the SPC

on the understanding that changes related to the indication in bipolar disorder are relevant to those Marketing Authorisation Holders applying to the new or amended indication. Based on the already well known safety profile for valproate, the MAHs are not in agreement with the submission of the Risk Management Plan. Furthermore, the MAHs refer to the fact that syrups and oral solutions are also approved for bipolar disorder in some Member States.

Having considered the detailed grounds for re-examination provided by the MAH in writing, the CHMP agrees that changes related to the indication in bipolar disorders are relevant to those Marketing Authorisation Holders applying to the new or amended indication, as applicable. Furthermore, when applying for the new indication the MAHs should submit a Risk Management Plan to the National Competent Authorities for assessment, as relevant. The CHMP agreed that the recommendations are applicable to all oral use formulations.

The scientific conclusions of the CHMP Opinion of 17 December 2009 were revised accordingly.

2.7 Changes to the Product information

A. Summary of Product Characteristics

Section 4.1 Therapeutic 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> for acute mania.

Section 4.2 Posology and method of administration

Manic episodes in bipolar disorder:

In adults:
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 and 2000 mg <valproate>. Patients receiving daily doses higher than 45mg/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.

In children and adolescents:
The safety and efficacy of {invented name} for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

Section 4.4 Special warnings and precautions for use

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of antiepileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for <active substance>. Therefore patients should be monitored for signs of suicidal ideation and behaviours and

appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Section 4.6 Pregnancy and lactation

This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). Women of child-bearing potential have to use effective contraception during treatment.

Section 4.8 Undesirable effects

Nausea, sedation, extrapyramidal disorders.

B. Package Leaflet

1. WHAT {INVENTED NAME} IS AND WHAT IT IS USED FOR
{Invented name} is a medicine for the treatment of (…) and mania.

{Invented name} is used in the treatment of

- Mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called "bipolar disorder". {Invented name} can be used when lithium can not be used.

2. BEFORE YOU TAKE {INVENTED NAME}

Take special care with {INVENTED NAME}
A small number of people being treated with anti-epileptics such as <active substance> have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Children and adolescents
Children and adolescents under 18 years of age:
{Invented name} should not be used in children and adolescents under 18 years of age for the treatment of mania.

Pregnancy and breast-feeding

You should not take this medicine if you are pregnant or a women of child-bearing age unless explicitly advised by your doctor. If you are a woman of child-bearing age, you have to use effective contraception during treatment.

3. HOW TO TAKE {INVENTED NAME}

Mania
The daily dosage should be established and controlled individually by your doctor.

Initial dose
The recommended initial daily dose is 750 mg.

Mean daily dose
The recommended daily doses usually range between 1000 mg and 2000 mg.

4. POSSIBLE SIDE EFFECTS

Nausea, sedation, extrapyramidal disorders.

3 OVERALL CONCLUSION

Having considered the overall submitted data provided by the MAHs in writing and, the CHMP concluded that the marketing authorisation of valproate/valproic acid containing products be amended.

Therefore, the CHMP recommended

> the variation to the terms of the Marketing Authorisation for the medicinal products referred to in Annex I, for which the relevant sections of the Summary of Product Characteristics and package leaflet are set out in Annex III to the opinion

The conditions affecting the Marketing Authorisations are set out in Annex IV.

Following consideration of the detailed grounds for re-examination provided by various MAHs in writing, the CHMP agrees that changes related to the indication in bipolar disorders are relevant to those Marketing Authorisation Holders applying to the new or amended indication, as applicable. Furthermore, when applying for the new indication the MAHs should submit a Risk Management Plan to the National Competent Authorities for assessment, as relevant. The CHMP agreed that the recommendations are applicable to all oral use formulations.

The scientific conclusions of the CHMP Opinion of 17 December 2009 were revised accordingly.

4 ANNEXES

The list of the names of the medicinal products, Marketing Authorisation Holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the Opinion.