# ANNEX II

# SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS PRESENTED BY THE EUROPEAN MEDICINES AGENCY

## SCIENTIFIC CONCLUSIONS

## OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF VALPROIC ACID/VALPROATE CONTAINING PRODUCTS (see Annex I)

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.

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.

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 (as valproic acid, sodium valproate, valproate semisodium) 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 valproic acid/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).

### 1. Efficacy

### 1.1 *Mania*

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.

These studies included nearly 2,500 patients, of whom 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.

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. In other words, 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.

According to the CHMP recommendation for valproate containing medicinal products the indication should be adapted as follows due to the limitations and shortcomings of the data from clinical trials as the analysis was based in relatively old clinical studies.:

> "*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*."

### 1.2 *Prevention of Recurrence of mood episodes*

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. *Post-hoc* analyses were done of the large Bowden study. 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 due to a mood episode, whereas the respective difference was not statistically significant compared to lithium treated patients.

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.

As conclusion the recurrence prevention of mania 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 events has not shown statistically significant differences. Evidence of efficacy of valproate in the prevention of mood episodes is thus not completely convincing based on the performed clinical studies.

### 1.3 *Chemical forms and formulations of valproate*

Based on the submitted data it cannot be concluded, that efficacy of valproate in the claimed indication is dependent on chemical form or formulation. 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. 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 Safety

### *2.1. Overall 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. No unexpected signals have been identified from post-marketing surveillance. 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*

Following the literature presented as well the post-marketing experience the adverse events of "nausea", "sedation" and "extrapyrimidal disorders" are proposed to be added to the Section 4.8 "Undesirable effects" of the SPC. The MAHs should look into their respective safety databases and add the approapriate frequence of occurrence to the above additional adverse events.

*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 pregnant women or 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 Pharmacovigilance Working Party concluded that any antiepileptic drug may be associated with a low risk of suicidal thoughts and behaviour. On the basis of the evidence available to the PhVWP, it was agreed that SPCs for all antiepileptics across the European Union should be modified with regard to suicidality with the addition of a warning.

### 2.2 *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 valproic acid/valproate authorised products applying to the new indication should submit a Risk Management Plan to the 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.

## 3 Re-examination

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 Decemeber 2009 were revised accordingly.

**GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS**

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, as amended, for valproic acid/valproate containing medicinal products initiated by The Netherlands.

- The Committee considered the grounds for re-examination submitted by various MAHs for valproic acid/valproate containing medicinal products on 13 April 2010 and the discussion within the Committee;

- The Committee considered all the available data submitted on efficacy and the safety for valproic acid/valproate containing products, in relation to the treatment of mania in bipolar disorder as well in the prevention of recurrence of mood episodes.

- The Committee concluded that valproic acid/valproate containing medicinal products have a positive benefit-risk ratio in the proposed amended indication "*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 the medicinal product for acute mania*".

- The Committee concluded that the Product Information of all valproic acid/valproate containing medicinal products should be amended to include information on the treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated and therefore recommended the amendments to the relevant sections of the Summary of Product Characteristic and Package Leaflet accordingly. In addition, the CHMP considered the safety profile of valproic acid/valproate in this indication and recommended some amendments to the Product Information in relation to the risk of suicidal ideation and behaviour, to the use in pregnancy and to the inclusion of nausea, sedation and extrapyramidal effects as undesirable effects.

  Furthermore, when applying to the new indication the MAHs should submit a Risk Management Plan to the NCAs for assessment, as relevant.

As a consequence, the CHMP has recommended the maintenance of the Marketing Authorisations for the medicinal products referred to in Annex I for which the amendments to the relevant sections of the Summary of Product Characteristics and Package Leaflets are set out in Annex III and in accordance to the conditions set out in Annex IV.