



Inclusion criteria	<ul style="list-style-type: none"> <li>- Male or female adolescents, 13 to 18 years of age, weighing over 40 kg at baseline, whose laboratory test results are normal, and who are capable of understanding the protocol.</li> <li>- Patients who have given their consent (along with a parent or legal guardian if under 18 years of age),</li> <li>- Presenting with the diagnostic characteristics of bipolar disorder in manic, mixed or hypomanic phase, established based on DSM IV,</li> <li>- With a score on the YMRS (Young Mania Rating Scale) <math>\geq 14</math> for manic phase or <math>\geq 10</math> for hypomanic phase.</li> </ul>
Study product	<p>Sodium divalproate (Dépakote®) enteric-coated tablets containing 250 and 500 mg of valproic acid, administered by oral route.</p> <p>The dosage is defined based on the patient's age, with an initial dose of 500 mg divided into 2 doses on the 1<sup>st</sup> day, then a stepwise increase of 250 mg/day to reach a minimum effective dose with regard to the desired clinical effect and safety, in about one week, not to exceed a maximum of 30 mg/kg/d.</p>
Duration of treatment	6 months
Evaluation endpoints	<p><u>Safety: Primary endpoint</u></p> <ul style="list-style-type: none"> <li>▪ Clinical safety:</li> <li>▪ Physical examination (heart rate, blood pressure, weight, height, BMI, neurological examinations) and systematic collection of adverse events at each visit.</li> <li>▪ Biological safety criteria: Blood assay (NFS, platelets, TCA). Liver test (transaminases, PT, fibrinogen, total and conjugated bilirubin, alkaline phosphatases, Gamma GT, serum ammonia), Lipid test (total cholesterol, HDL-c, triglycerides, calculated LDL-c), Fasting blood glucose level, serum urea, serum creatinine, blood electrolytes, serum protein, TSH.</li> <li>▪ Plasma concentrations of valproic acid in the event of occurrence of an adverse event caused by the study treatment, or in the event of early withdrawal from the study.</li> </ul> <p><u>Efficacy: Secondary endpoints:</u> YMRS score, CDRS-R score, CGI score</p>
Method of analysis of the primary endpoint planned in the protocol	<ul style="list-style-type: none"> <li>- <b>Clinical safety:</b> Number and percentage of patients who present with at least one adverse event per organ-system.</li> <li>- <b>Biological safety:</b> Qualitative analysis as compared to normal laboratory test values, taking patients' age into account (at least one value outside of normal when under treatment).</li> </ul>

Results on safety	<ul style="list-style-type: none"> <li>• Adverse events: 23 patients out of 24 presented with at least one adverse event during the study. 14 patients (58%) presented with an event that was considered by the investigator to be caused by the treatment with Dépakote®. Headaches and digestive disorders known to be side effects of the product were the most commonly listed events. 6 patients presented with a serious event: two patients attempted suicide, four patients presented with symptoms related to their bipolar disorder, in the form of depression (1 patient), mania or hypomania (3 patients). Only one event was considered by the investigator to be related to the study treatment. Two patients interrupted their treatment early following an adverse event:</li> <li>• Clinical data: The treatment does not seem to have any impact on the cardiovascular parameters. Patients' change in body weight over the course of the study seems to confirm the known effects of Dépakote® on weight gain.</li> <li>• Laboratory test data: Except for in one case (reduction in fibrogen level), the investigators involved in this study considered that treatment with Dépakote® did not have any clinically significant impact on the patients' laboratory test parameters. The occurrence of moderate hyperammonemia (without alteration of laboratory tests on liver function) was the most common event (8 patients, or 1/3 of the population).</li> </ul>
Results on efficacy	<p>The results obtained on the psychometric scales used in the evaluation of manic and depressive symptoms and in the evaluation of global clinical impressions are provided for information purposes only, and do not allow any statistically relevant conclusions. Nonetheless, the data reported during the follow-up seem to confirm the efficacy of Dépakote® in the management of bipolar disorder in adolescents. This efficacy seems to occur quickly (within the first 15 days of treatment).</p>
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