

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-267

CROSS DISCIPLINE TEAM LEADER REVIEW

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March, 2008

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products

TO: File NDA 22-267 (This overview should be filed with the 09-24-2007 submission.)

SUBJECT: Depakote ER[®] (divalproex sodium) for the Treatment of Bipolar Disorder, Acute Manic or Mixed Episodes, in children and adolescents aged 10 to 17 yrs

1. BACKGROUND

Depakote ER[®] (divalproex sodium) is an anticonvulsant approved for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features in adults. It is also approved for both mono-therapy and adjunctive therapy in complex partial seizures, complex absence seizures and adjunctively for multiple seizure types in patients aged 10 years of age or older. In addition, Depakote ER[®] tablets are indicated for prophylactic treatment of migraine headaches in adults.

Depakote ER[®] is available as 250 and 500 mg strength tablets. Depakote ER is an extended-release product intended for once-a-day oral administration. Based on data from a placebo-controlled adult mania trial, the recommended initial dose is 25 mg/kg/day given once daily. The maximum recommended dosage is 60 mg/kg/day. Dose adjustments should generally be made based on clinical response with a trough plasma concentration between 85 and 125 µg/mL.

On August 9, 2002, the Agency issued a pediatric Written Request to Abbott Laboratories, the sponsor for Depakote ER[®] tablets to conduct efficacy and safety pediatric studies in patients with bipolar, migraine prophylaxis and epilepsy, and submit information from the pediatric studies. On January 31, 2006, a revised Written Request was issued to amend the time-frame whereby all data from the studies performed under the WR must be received by the Agency from August 6, 2005 to October 7, 2007.

Pursuant to the WR, the sponsor submitted data from the completed bipolar studies to the Agency on September 24, 2007 under NDA 22-267. The efficacy of Depakote ER[®] for the treatment of mania in the child and adolescent population was from one single randomized double blind, placebo controlled flexible dose study (M01-342). The safety data of Depakote ER[®] in adolescent mania was from study M01-342 with longer term safety data derived from a six-month open label extension study (M02-555) and an additional six month open label study (M03-647).

The sponsor also submitted data from pediatric epilepsy and migraine trials in supplemental NDA (SE5-015) to NDA 21-168, crossed referenced to other depakote NDAs. The division of neurology

products (DNP) is the lead division for this product. Currently, DNP is reviewing new clinical pharmacology and relevant clinical study information for respective indications.

The pediatric bipolar clinical data submitted under NDA 22-267 has been reviewed by Dr. Mark Ritter, DPP-Medical Officer (review dated 2/21/2008).

2.0 CHEMISTRY

No new CMC issue in this NDA that would require a review.

3.0 PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology issues that would require a review.

4.0 CLINICAL PHARMACOLOGY

The sponsor conducted literature review based on the fact that adequate pharmacokinetic information in pediatric patients is available in the literature. No formal pharmacokinetic studies were performed under this submission. The submitted information has been reviewed by the Office of Clinical Pharmacology under NDA21-168/SE5-015 to DNP.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of a single study (study M01-342) to evaluate the efficacy and safety of Depakote ER in the treatment of Bipolar Disorder, Acute Manic or Mixed Episodes, in children and adolescents aged 10 to 17 yrs. Since the sponsor is not seeking for efficacy claim in the labeling as efficacy was not established for Depakote ER[®] in this study, we did not ask the Division of Biometrics to conduct any confirmatory analysis.

5.1.2 Summary of Study Pertinent to Efficacy Claim

Study M01-342

The objective of the study was to demonstrate the efficacy and safety of Depakote ER in the treatment of acute mania or mixed episodes in children and adolescents aged 10-17 years old with a current bipolar I disorder diagnosis according to DSM-IV criteria. All subjects were assessed using the Washington University at St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) administered by a qualified mental health professional with confirmation of diagnosis performed by a child psychiatrist.

This study consisted of an initial screening and washout period (with the exception of stimulant medication) lasting 3 to 14 days. This was followed by an outpatient, 4- week, double-blind treatment in which patients were randomized to either placebo or Depakote ER. The initial dose of Depakote ER was targeted to 15mg/kg/day (not to exceed 750mg/day on day 1). Dosage increases

of 250mg were permitted at the discretion of the investigator every 1-3 days to achieve a maximum clinical effect and/or a serum valproate level within the range of 80-125mcg/ml. The maximum dose that was allowable for this study was 35mg/kg/day. During the study, the subjects were evaluated at each on-site visit being scheduled at seven day intervals. At study conclusion, patients were offered an optional one-week taper period.

The study was conducted at 24 U.S. centers. A total of 229 patients were screened; 151 were randomized with 150 ITT population taking at least one dose of Depakote ER (76 subjects) or placebo (74 subjects). 82% for placebo and 74% for Depakote ER patients completed the study. 33 subjects discontinued; the most common reasons for discontinuation were adverse events, withdrawal of consent and lost to follow up.

The subjects enrolled were mostly Caucasian (74%); mean age of 12.9 yrs. Male comprised about 60%. There seemed to be no significant differences in demographic characteristics among the treatment groups. The mean total YMRS scores at the baseline were similar between the treatment groups: 31.1 in the drug group and 31.3 in the placebo group. Both placebo and Depakote ER® groups also had similar Bipolar I presentations based on DSM-IV criteria in that approximately 50% of the presentations were mixed.

Primary efficacy was assessed by the change from baseline scores to the final evaluation [i.e. last observation carried forward (LOCF)] on the Young Mania Rating Scale (YMRS) for the intent to treat population (ITT). Two-way ANCOVA was used with baseline value covariate with treatment and investigator as factors.

The table below showed negative primary efficacy result for Depakote ER as compared to placebo.

Table: Results for Mean Change from Baseline to endpoint for the YMRS (ITT)

DAY OF MEASUREMENT	PLACEBO (N=70)	DEPAKOTE ER (N=74)	P-VALUE*
Baseline (SD)	31.3 (7.47)	31.1 (6.78)	0.716
Change from baseline to endpoint (SD)	-8.0 (10.56)	-8.5 (8.84)	0.548

Comment: Dr. Ritter considered this a negative study for Depakote ER, and I agree with him.

5.1.3 Comments on Other Important Clinical Issues

Dose response relationship

This study was a flexible dose study. Although the efficacy data showed negative results for Depakote ER, mean daily dose of 1457.2 ± 532.9 mg/day (range 750-3250mg) with average plasma concentration of 27.1 ± 6.3 mg/kg/day was achieved in the Depakote ER group.

Secondary efficacy variables

There were no key secondary variables pre-specified in this study. The sponsor did perform secondary efficacy assessments using the Children's Global Assessment Scale (C-GAS), the

Clinical Global Impression Scale severity and Improvement, the Children's Depression Rating Scale Revised (CDRS-R), the overt aggression Scale-Modified (OAS-M), the Caregiver Strain Questionnaire (CGSQ) and the ADHD-RS-IV Home version rating scale. A lack of efficacy was also demonstrated on all secondary measures of efficacy as well.

Subgroup analyses of efficacy data

No exploratory subgroup analyses were performed in order to detect subgroup interactions on the basis of gender, race or age.

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analyses did not show efficacy of Depakote ER in the treatment of bipolar disorder, acute manic or mixed episodes in children and adolescent patients aged 10-17 yrs.

5.2 Safety Data

In the 4 week randomized placebo-controlled bipolar trial, a total of 76 subjects (aged 10-17 yrs) received Depakote ER while 74 subjects received placebo.

A total of 292 bipolar patients were treated in 6-month open-label studies (study M02-555: 66 subjects; M03-647: 226 subjects). Regarding 6 month exposure data, there were 119 subjects (study M02-555: 20 subjects; M03-647: 99 subjects).

No deaths occurred during the clinical trials. There were three (3) serious adverse events that occurred during the placebo-controlled trial leading to hospitalization: One patient from each treatment group was hospitalized for suicidal ideation and one patient in the Depakote ER[®] treatment group hospitalized and treated in the intensive care unit for symptomatic hyperammonemia with disorientation.

5.2.1 Common and drug-related adverse reactions

Those events that were common (>5% frequency) and drug related (frequency rate at least twice the rate of placebo) that occurred in the placebo-controlled pediatric bipolar trial are nausea (9.2%), upper abdominal pain, somnolence, gastritis, rash and increased ammonia.

5.2.2 Adverse events of special interest

In addition to routine safety monitoring, the Written Request specified that hepatotoxicity, hyperammonemia, pancreatitis, thrombocytopenia, rash, cognitive/neuropsychiatric adverse events, movement assessments and effects on growth be specifically monitored. These assessments were performed during the six-month open label trial.

One patient was discontinued from the open label study without clinical sequelae on day 57 for increased liver function tests which ultimately normalized upon cessation of study drug. Also, There were no SAEs associated with pancreatitis or pancreatic disease, nor were there discontinuations due to elevated amylase levels.

One subject in the open label mania trial was discontinued from the study on day 20 as a result of an erythematous and pruritic rash. There were, however, no serious dermatological reactions that were reported during any mania trial.

Overall, depakote administration did not impair cognitive verbal and performance measures during administration as evidenced by the slight mean change improvement in all scores using the Wechsler Abbreviated Scale of Intelligence (WASI) administered at baseline and at the final visit. However, due to the lack of a placebo group, it is difficult to interpret such data.

There were no additional increases in the rates of abnormal movements at study endpoint in the open label trial. The adverse events observed during these pediatric open-label studies were found to be similar to safety profile as already described in the Depakote ER labeling.

5.2.3 Laboratory Tests

There was a statistically significant decrease in mean change from baseline platelet, total protein and white blood cell counts in Depakote ER[®] treated patients as compared to placebo patients. Serum ammonia, uric acid and blood urea nitrogen levels also showed statistically significant increases from baseline in the Depakote ER[®] subjects compared to placebo. 7% of subjects (14/190) that had normal baseline ammonia levels had at least one potentially clinically significant ammonia level (defined as >90 mcmmol/L), however no SAEs were reported in any of these patients.

5.2.4 ECG, vital sign and weight changes

There were no significant outliers noted in vital sign or ECG parameters during the placebo-controlled trial in both groups. However, patients that were assigned to Depakote ER[®] had a statistically significant 2.3 lbs increase in weight compared to 0.8 lbs in placebo and 0.5 unit vs. 0.1 unit BMI increase as compared to placebo treated patients respectively.

5.2.5 Conclusion Regarding Safety Data

Overall, this NDA submission revealed no new safety concerns with Depakote ER in pediatric bipolar population. The safety data from the clinical studies should be adequately described in the labeling.

6.0 WORLD LITERATURE

Dr. Ritter cited relevant review of the literature pertinent to this submission in his review. I did not see any new safety concerns with Depakote recently published in the literature.

7.0 FOREIGN REGULATORY ACTION

I am not aware that the sponsor provided any foreign regulatory action information regarding use of Depakote ER in pediatric bipolar disorder.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

No inspections were conducted due to the lack of positive efficacy results.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

The sponsor has provided labeling in new PLR format. According to the new law in effect, description of negative pediatric studies must be included in the labeling. The sponsor's proposed language for should be modified. All the labeling changes should be negotiated with the sponsor. A copy of final agreed-upon labeling should be included in the action letter.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient safety and efficacy data from bipolar mania trials in patients aged 10-17 yrs in pursuant to the Pediatric WR. The terms for pediatric exclusivity requirement were met as was determined by the pediatric exclusivity board.

I agree with Dr. Ritter's recommendation that neither an approval/approvable nor a non-approval action is indicated as the sponsor is not seeking a claim for the treatment of pediatric bipolar disorder due to lack of efficacy seen in the single double-blind, placebo controlled trial. I believe we should be able to adequately describe the study design, lack of efficacy resulting from the study along with safety data obtained in the pediatric trials in the labeling. We should send our action letter provided that we reach an agreement with the sponsor regarding the language in the labeling.

cc: HFD-130/Laughren/Mathis/Ritter/Bates

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/s/

Ni Aye Khin
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MEDICAL OFFICER