CLINICAL REVIEW

Application Type	NDA
Submission Number	22-267
Submission Code	Type 6
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Reviewer Name	Mark Ritter, MD RPh
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Established Name	Divalproex sodium
Trade Name	Depakote ER®
Therapeutic Class	anticonvulsant
Applicant	Abbott
Priority Designation	P
Formulation	Extended release
Dosing Regimen	Daily
Indication	Treatment of acute mania
Intended Population	Adolescents aged 10-17 years old.

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The trials completed under this NDA submission were submitted pursuant to a Written Request to obtain safety and efficacy data for the indication of acute adolescent mania associated with bipolar disorder. The terms of the Written Request were met. 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, neither an approval/approvable nor a non-approval action is indicated for this NDA submission.

Due to the lack of efficacy seen in this study, the Depakote ER® label will include a description of the pediatric study design and lack of efficacy resulting from the study. In addition safety and adverse event information obtained from the study will also be included. Please refer to section 10.2 for a full review and recommendations on labeling.

1.2 Recommendation on Postmarketing Actions

As clinical controversy continues to surround the phenotypic presentations of pediatric bipolar disorder, it is recommended that additional pharmacotherapy studies on the NIMH defined "narrow" phenotype of pediatric bipolar disorder, characterized as distinct, episodic elevations in mood with grandiosity, be conducted as efficacy was not established for the mixed phenotype population that was selected for this NDA submission.

The continued use of stimulant medication for clinically stable co-morbid attention deficit/hyperactivity disorder (ADHD) patients was a confounding factor in this study. As significant, objectively determined ADHD symptoms were present at baseline despite continued stimulant treatment in approximately 23% of patients with 67% meeting diagnostic criteria for ADHD, it is recommended that future pediatric bipolar studies exclude concomitant ADHD medication use during trials and limit baseline ADHD symptom severity via objectively defined measures *a priori* prior to subject randomization.

Finally although the mean modal doses used in this study were within the pre-specified range of doses selected, the mean serum valproate concentration obtained in this flexible dose trial suggests that the doses used were, on average, able only to achieve the lowest level of the protocol-specified therapeutic concentration range of 80mcg/ml. Therefore this reviewer suggests that additional fixed dose studies targeted at low, medium and high mean serum valproic acid ranges be considered to explore whether a dose-response relationship exists.

1.2.1 Risk Management Activity

No additional Risk Management plan or recommendations are warranted at this time.

1.2.2 Required Phase 4 Commitments

There are no Phase 4 commitments required at this time.

1.2.3 Other Phase 4 Requests

None at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Pursuant to the Written Request, the sponsor conducted a single 4-week outpatient, randomized (1:1 Depakote ER® to placebo), double blind, parallel-group, placebo-controlled study of 150 pediatric patients aged 10-17 years of age with a diagnosis of bipolar disorder as defined by the Washington University Kiddie-Schedule for Affective Disorders and Schizophrenia (WASH-U K-SADS) instrument. With the exception of medication being used to treat co-morbid ADHD), all patients were titrated off their current medication regimen during a 3 to 14 day screening/washout period.

Additionally two (2) 6-month open label studies were conducted to obtain additional data on the tolerability and safety of Depakote ER® use for pediatric bipolar disorder. Sixty-six (66) patients from the above placebo controlled study who either completed the study or terminated early elected to continue participation in the first 6-month open label safety study. In order to meet the terms of the Written Request for data on at least 100 patients over a 6-month period of time, an additional second open label safety study was performed, with an additional 226 patients enrolled. At the end of six months, a total of 119 patients were exposed to 6 months of Depakote ER® (20 patients from the extension study and 99 subjects from the second open label study).

1.3.2 Efficacy

Primary efficacy in the pivotal study 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). There were no key secondary variables identified in this study.

Study results showed that Depakote ER® was not effective for the treatment of acute mania associated with bipolar disorder (broad phenotype) in children aged 10-17 years of age as compared to placebo based on the results from the single four week, flexible dose, double-blind, and placebo controlled study.

1.3.3 Safety

Placebo Controlled Study
No deaths occurred during any study period. There were three (3) serious adverse events (1 placebo, 2 Depakote ER®) that occurred during the placebo-controlled trial leading to hospitalization: One patient from each treatment group was hospitalized for suicidal ideation (prior history of suicidal behavior) and one patient in the Depakote ER® treatment group hospitalized and treated in the intensive care unit for symptomatic hyperammonemia with disorientation.

During the placebo controlled trial, four (4) valproic acid patients withdrew from the study for adverse events [5.2% (4/76)] compared with three (3) [4% (3/74)] on placebo: two (2) of the withdrawals from the valproic acid treated group were the patients who also experienced an SAE. The remaining two (2) non-SAE related adverse events that occurred in the valproic acid group leading to drop-out were 1.) Migraine and 2.) Depression.

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 upper abdominal pain, gastritis, nausea, increased ammonia, somnolence and rash.

During the placebo controlled trial 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.

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. There was no effect seen on height during this study in either group.

Six-Month Open Label Studies

The sponsor performed adequate safety assessments as requested by the Written Request during the 6-month open label safety studies. 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 and adequately assessed during the six-month open label trial.

The adverse events seen during the open label studies were found to be similar to the known safety profiles as already described in current labeling. In addition, the use of Depakote ER did not appear to impair cognitive performance, worsen behaviors, or lead

to an increased rate of abnormal movements during the 6-month open label studies, though without a placebo group one cannot determine whether or not the results seen in these measures are consistent with changes that would have been seen in placebo treated subjects.

1.3.4 Dosing Regimen and Administration

Pursuant to the Written Request, a literature search and analysis was performed on available dosing and pharmacokinetic information.

As there was insufficient data to conclude efficacy for Depakote ER® in the treatment of adolescent mania, the sponsors proposed [redacted].

1.3.5 Drug-Drug Interactions

Pharmacodynamic studies were not required under the Written Request. Please refer to the current product labeling and previous Agency reviews for details regarding drug-drug interactions.

1.3.6 Special Populations

The sponsor did not conduct any pharmacokinetic studies in patients with cardiovascular, hepatic or renal diseases.

2 INTRODUCTIONS AND BACKGROUND

2.1 Product Information

Depakote ER® is pharmacologically classified as an anticonvulsant. The pharmacologically active ingredient of Depakote ER®, divalproex sodium, disassociates into two valproate ions *in vivo*. Although the pharmacological action of valproate is unknown, it has been suggested that the activity is related to valproic acid's ability to increase brain levels of the inhibitory neurotransmitter gamma amino butyric acid (GABA), thus increasing the seizure threshold and the neuronal firing threshold in overly active neurons.

2.2 Currently Available Treatment for Indications

Depakote ER® tablets are currently FDA approved for the treatment of acute mania. In addition they are approved for both mono-therapy and adjunctive therapy for the treatment of complex partial seizures, complex absence seizures and adjunctively for multiple seizure types in patients aged 10 years of age or older. Depakote ER® tablets are also indicated for prophylactic treatment of migraine headaches in adults.

Currently the only Agency approved treatments for pediatric bipolar disorder are lithium in children aged 12 years and older, and risperidone in children aged 10-17 years of age.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in Depakote ER®, divalproex sodium, is available under the brand names DEPAKENE® (valproic acid capsules and solution), Depakote Sprinkle capsules® (divalproex sodium) and Depakote Delayed release tablets® (divalproex sodium). Depakote Delayed release tablets® and Depakote ER® are both approved for similar indications. However DEPAKENE® and Depakote Sprinkle capsules® are currently only FDA approved to treat complex partial seizures and simple and complex absence seizures either as mono-therapy or adjunctive therapy.

2.4 Important Issues with Pharmacologically Related Products

To date there have been no consistent regulatory issues identified as being related to the anticonvulsant class of medications. However some individual compounds of the anticonvulsant class have shown to have specific adverse events associated with use which has been adequately addressed in their current labeling.

2.5 Presubmission Regulatory Activity

Pursuant to the requirements set forth in the Best Pharmaceuticals act for Children (BPAC), the sponsor submitted a Proposed Pediatric Study Request (PPSR) on June 22, 2001 for Depakote ER®. On August 9, 2002, the Agency issued a pediatric Written Request to the sponsor for Depakote ER® tablets to submit information from pediatric bipolar, migraine prophylaxis and epilepsy studies.

On January 31, 2006, a revised Written Request was issued as the previously issued Written Request had expired on August 9, 2005. The subsequent Written Request thus amended the time-frame (whereby all data from the studies performed under the Written Request must be received by the Agency) from August 6, 2005 to October 7, 2007.

The completed studies performed by the sponsor pursuant to the Written Request were finally submitted to the Agency on September 24, 2007.

2.6 Other Relevant Background Information

No other relevant pediatric background information is available for Depakote ER® as this formulation has not received a pediatric mania indication in any other country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

At the time of this review there do not appear to be any major CMC issues pending. Please see the formal CMC review for further details and analysis.

3.2 Animal Pharmacology/Toxicology

Although the formal pharmacology/toxicology review is not available, no issues have been raised to this reviewer with regards to the approvability of Depakote ER® from a pharmacology/toxicology perspective.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Pursuant to the Agency's Written Request, the efficacy of Depakote ER® for the treatment of mania in the child and adolescent population was determined through one single phase 3 study (M01-342, a randomized double blind, placebo controlled flexible dose study).

The safety of Depakote ER® in adolescent mania was determined 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). Due to the lack of enrollment into study M02-555, study M03-647 was conducted to satisfy the requirement set forth in the Written Request to evaluate safety in at least 100 patients for 6 months.

4.2 Tables of Clinical Studies

Table 1: Depakote ER® Table of Studies

Phase 3 Studies	
M01-342 Flexible Dose	A maximum six–week, outpatient, multicentered, double-blind, parallel-group, placebo controlled, randomized (1:1 drug: placebo), flexible dose study of 150 adolescent patients (ages 10-17 years of age) with a current clinical diagnosis of bipolar I disorder, manic or mixed (according to DSM-IV criteria using the WASH U-KSADS instrument) treated with Depakote ER® for four weeks with an optional one-week taper period at doses used to achieve a clinical effect and/or serum valproate level of 80-125 mcg/ml or maximum of 35mg/kg/day.
M02-555 Open label Safety	Six month multicentered, open label extension safety study of study M01-342 in 66 enrolled adolescent patients with mania.

M03-647 Open label Safety	Six month multicentered, open label safety study in 226 treated adolescent patients with mania (according to DSM-IV criteria using the K-SADS-PL instrument) associated with Bipolar I disorder

4.3 Review Strategy

Table 2 below provides a listing of documents that were reviewed during the NDA review process.

Table 2: Items Utilized in this review

SUBMISSION DATE	ITEMS REVIEW
September 24, 2007	-Study reports: M01-342, M02-555, M03-647 -Proposed labeling -Written Request -Financial Disclosure Certification -Application Summary -Case Report Tabulations (.xpt files) -Case Report Forms

4.4 Data Quality and Integrity

An investigation was not performed by the Division of Scientific Investigations (DSI) due to the lack of positive efficacy results.

4.5 Compliance with Good Clinical Practices

Studies M01-342, M02-555 and M03-647 were conducted according to the Declaration of Helsinki and amendments. All subject information was documented and stored using Good Clinical Practices (GCP) as delineated in the Health Insurance Portability and Accountability Act (HIPAA) of 1997.

4.6 Financial Disclosures

[redacted] study [redacted], received significant payments during the study period that were in excess of $25,000, in addition to the payments for conducting study [redacted].

[redacted], received significant payments during the study period that were in excess of $25,000, in addition to the payments for conducting study [redacted].

[redacted] received significant payments during the study period that were in excess of $25,000, in addition to the payments for conducting study [redacted].

, received significant payments during the study period that were in excess of $25,000, in addition to the payments for conducting study .

Since the pivotal study did not establish efficacy, any financial bias that may have been present was insufficient to influence the results in favor of the drug.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Note: Please see the biopharm/clinical pharmacology review for a more detailed pharmacokinetic review

Pursuant to the Written Request, adequate pharmacokinetic information in pediatric patients is available in the literature and hence no formal pharmacokinetic studies were performed under this submission. As a lack of efficacy was seen in all the submitted sponsor studies, the sponsor-submitted However, for completeness, this reviewer had conducted a brief review of pertinent points from the summary of the sponsor's pharmacokinetic analysis. For completeness, the sponsor-proposed pharmacokinetic labeling is discussed within section 10.2 of this review.

The sponsor conducted a Medline/Pubmed from 1965 to June 2007 to identify pediatric and child pharmacokinetic studies of valproic acid. The search yielded seven single dose pharmacokinetic studies in pediatric epilepsy patients (two mono-therapy and five polytherapy); 17 reports of pediatric epilepsy patients on repeated dose valproic acid mono-therapy and 13 reports on repeated dose polytherapy. Seven reports of the population pharmacokinetics of valproic acid in children were also included in this analysis, although all of these studies were performed outside of the United States. Previously submitted pharmacokinetics data in kids from NDA 20-593 and NDA 18-723 is also included as part of this submission.

Infants appear to have a remarkable increase in valproic acid clearance over the first two months of age that gradually increases until age 36 months (109% higher clearance compared to adult clearance). At age 3 the metabolism of valproic acid appears to gradually decline and reaches adult levels by puberty (26% higher clearance compared to adult clearance). As such, valproic acid doses in children are generally higher on a mg/kg basis than in adults.

Taking various age related factors into account for valproic acid clearance and metabolism, the sponsor has combined the clearance/demographic pediatric data in the literature with existing data from adult epilepsy patients with concomitant enzyme-inducing drugs in order to support proposed .

Half-life
The reported mono-therapy elimination half life in the adult literature is approximately 14-16 hours which decreases to 9-12 hours in the presence of concomitant enzyme inducing medication use. Using the estimated values for clearance and Vd obtained through review of the pediatric literature, the sponsor estimates the following elimination half-lives in children and adults with and without the concomitant presence of an enzyme inducing medication:

Figure 1: Half Life of Valproic Acid by age

Age	Half-Life (h)	
(years)	Uninduced	Induced
3	9.0	5.2
4	9.7	5.6
5	10.4	6.0
6	11.3	6.4
7	12.1	6.9
8	13.0	7.4
9	13.9	8.0
10	15.0	8.6
Adult	15.7	9.0

Drug Interactions
Based on the existing pediatric studies and data, valproic acid administration in children is anticipated to have similar drug-drug pharmacokinetic interactions compared to the adult population, namely decreased valproic acid levels in the presence of enzyme inducers and increased levels of lamotrigine of up to 85% when given in the presence of valproic acid.

Analysis of the pediatric data
An analysis of the pediatric literature data performed by the sponsor showed that valproic acid clearance is nonlinearly rated to age even after adjusting the clearance for body weight. There was no significant difference in the effect of concomitant enzyme-inducing medication use on the clearance rates between children and adults. Although the BSA-normalized clearance values was the optimal was to adjust for clearance, all dosing guidelines were developed on the data from BW-normalized clearances as clinicians more frequently use BW over BSA values to dose pediatric patients. Using a maintenance concentration of 75mcg/ml as the basis for repeated dosing guidelines, the sponsor delineated the findings from the analysis as seen below in its simplified form:

Figure 2
Estimated Body Weight-Normalized VPA Daily Doses, Rounded to Multiples of 10 mg/kg/day, Required to Maintain Average Concentrations of 75 μg/mL in 3 to 10 Year-Old Children

Age	Daily Dose (mg/kg/day)	
(years)	Uninduced	Induced
3	30	60
4	30	50
5	30	50
6	30	40
7	20	40
8	20	40
9	20	40
10	20	30

5.2 Pharmacodynamics

There is not expected to be a difference in the pharmacodynamic properties of valproic acid in adults and children.

5.3 Exposure-Response Relationships

The flexible dose design of the submitted single mania study precludes an analysis of a pediatric exposure-response relationship at this time.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The submitted pediatric study (M01-342) was performed pursuant to the Written Request, for the treatment of 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 using the Washington University at St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS).

6.1.2 Methods

Pursuant to the Written Request, a single randomized, double-blind, placebo controlled trial was performed to evaluate the efficacy of valproic acid in the treatment of adolescent mania.

Protocol M01-342
This multicentered U.S. study was conducted at 24 sites from April 1, 2003 to November 22, 2005 with Scott Segal, MD as the coordinating investigator.

Two amendments to the protocol were submitted with the following notable changes:

- June 18, 2003 amendment clarified that all subjects will undergo a WASH-U-KSADS administered by a qualified mental health professional with confirmation of diagnosis performed by a child psychiatrist.

- May 26, 2004 amendment revised the exclusionary criteria to permit patients with (in addition to ADHD, OCD, oppositional defiant disorder, conduct disorder and panic disorder) co morbid enuresis, encopresis, parasomnias, agoraphobia, specific phobia, social phobia or separation anxiety disorder to enter the study. Also the subsection Psycho education (which provided standardized materials to families/children about the diagnosis, symptomatology and treatment of bipolar disorder at each study visit) was deleted from the study.

The list of clinical investigators who took part in the efficacy study are listed in table 27 in the appendix.

6.1.3 General Discussion of Endpoints

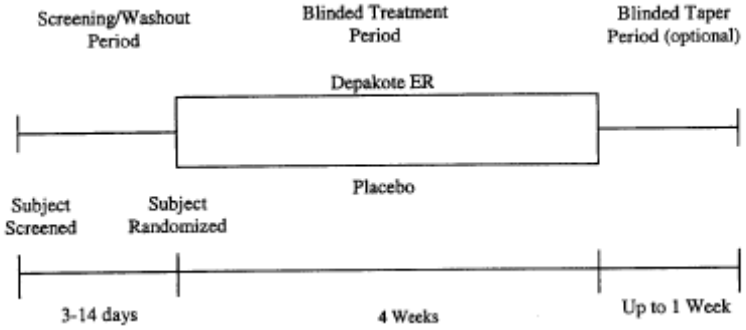
Primary efficacy was assessed by the change from baseline scores to the final evaluation [i.e. last observation carried forward (LOCF)] on the YMRS for the intent to treat population (ITT). The YMRS has reported validity and reliability and has been previously accepted by the Agency as a standard measure for measuring mania symptom response in clinical trials. This measure also has wide acceptance and use within the pediatric population.

There were no key secondary variables identified 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. An analysis of these efficacy measures as measured by change from baseline to final evaluation was also performed.

6.1.4 Study Design

Study M01-342 was an outpatient, randomized (1:1), double-blind, placebo-controlled, parallel group, flexible dose study with a blinded treatment period of four weeks. An initial screening and washout period (with the exception of stimulant medication) lasting 3 to 14 days preceded the 4 week outpatient treatment period. At study conclusion, patients were offered an optional one-week taper period. The design schematic is provided below.

Figure 3: Study Design



The initial dose of valproic acid 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.

There were a minimum six (6) required, on-site study visits during the study with each visit being scheduled at seven day intervals. Scheduled study assessments (see section 6.1.4.2 for assessments) were performed during these on-site visits. Approximately 3-4 days after each on-site visit, the patient's caregiver was contacted at a scheduled time by the study investigator to: 1.) Evaluate and adjust the dose of the study medication as appropriate; 2.) To inquire as to any possible adverse events; and 3.) To gauge the subject's response to the medication.

In order to preserve the study blind from valproate concentrations being reported to the investigators during the first 7-14 days of the study, a corresponding sham telephone call would be placed to a different investigator about a placebo subject at the same time point in the study to report that the level was high or low. Every investigator that received a call from the laboratory regarding valproate levels used clinical judgment to determine if an increase or decrease in dose was clinically warranted.

6.1.4.1 Patient Samples

The following inclusion criteria were applied for this study:

- 10-17 year old males and non pregnant, non lactating females weighing at least 60 lbs.
- A current psychiatric diagnosis of bipolar I, manic or mixed episode, based upon the WASH-U-KSADS interview and DSM-IV criteria.
- a YMRS score $\geq$20 at both screening and at the time of randomization
- Good physical health

Patients were excluded from the study if:

- females of childbearing potential were not using an effective method of birth control
- patients had an Axis I disorder other than ADHD, OCD, oppositional defiant disorder, conduct disorder, panic disorder, enuresis, encopresis, parasomnias, agoraphobia, specific phobia, social phobia or separation anxiety; or the subject has an Axis II disorder that would interfere with study procedures or interpretation of results.
- patients met DSM-IV criteria for substance abuse within the month prior to screening; met criteria for substance dependence within three months prior to screening; or exhibited signs of drug or alcohol intoxication or withdrawal at time of randomization.
- the mixed or manic episode was drug induced (e.g. SSRI) or medically related
- the patient was expected to require hospitalization for the current manic or mixed episode; or was violent, homicidal, or suicidal that, in the investigators' judgment, was at significant risk of hurting self or others.
- the patient had a history of any progressive CNS disease, seizures (or suspected of having seizures), hepatitis, pancreatitis or urea-cycle disorder.
- the patient had a platelet count $\leq$ 100,000/microliter and/or AST or ALT $\geq$2 times upper limit of normal.
- the patient had received significant exposure to Depakote, defined as > 10mg/kg/day for at least one week or failed an adequate trial of Depakote for a manic or mixed episode within the past 12 months.
- the patient was taking a protocol approved ADHD medication that has either not been stable for at least 3 months prior to randomization; was expected to be dose adjusted during the trial, or was exacerbating the mood symptoms (atomoxetine and pemoline use was not permitted during this study).
- the patient had a positive urine drug screen for drugs of abuse (including cocaine, phencyclidine, opiates, amphetamines, barbiturates and benzodiazepines, but *excluding* tetrahydrocannabinol [THC]) at screening unless the detected drug has been appropriately prescribed for the patient.

Of note, patients with a positive urine drug screen at screening for tetrahydrocannibinol were not excluded from participating in the study, as well as no urine drug testing of patients at the time of randomization or at any point beyond the initial screening in this trial. In addition, the use of substances and/or alcohol during the trial was not a delineated criterion for subject removal for this trial.

6.1.4.2 Schedule of Assessments

The table below delineates the assessment schedule pertaining to this study.

Study Procedures	Screening (3-14 Days)	Day 1[e] (Randomization)	Day 7	Day 14	Day 21	Day 28/ Premature Discontinuation	Taper Period[g] (Optional)
Informed Assent & Consent	X[a]						
Medical and Psychiatric History	X	X[f]					
Physical Exam[b]	X					X	
Weight	X	X				X	
ECG	X					X	
Vital Signs	X	X	X	X	X	X	
Urine Pregnancy Test[c]	X	X		X		X	
Hematology & Chemistry	X			X		X	
Ammonia	X					X	
Urinalysis	X					X	
TSH, PT, PTT, HBsAg, HCV, Urine Drug Screen	X						
Total Valproate level			X	X		X	
WASH-U-KSADS	X						
YMRS	X	X	X	X	X	X	
CGI		X	X	X	X	X	
CDRS-R		X		X		X	
C-GAS, OAS-M, ADHD Rating Scale-IV, CGSQ		X				X	
Psychoeducation		X	X	X	X		
Dispense Study Drug		X	X	X	X	X[g]	
Record Adverse Events	X[d]	X	X	X	X	X	X
Record Concomitant Medication	X	X	X	X	X	X	X
Telephone contact		X[h]	X[h]	X[h]	X[h]		

[a] Must be obtained prior to any study procedures, including discontinuation of medications.
[b] Including height.
[c] Urine pregnancy tests will be given to female subjects only.
[d] Record Serious Adverse Events only.
[e] Perform Day 1 procedures prior to dosing.
[f] Record any changes that have occurred since screening.
[g] For subjects tapering off study medication (optional).
[h] The investigator will contact the subject's caregiver at a scheduled time 3-4 days after the visits for Day 1, Day 7, Day 14, and Day 21.

6.1.4.3 Concomitant medication use

Subjects were permitted to continue stimulant treatment for their ADHD provided that the dosing regimen was stable for at least 3 months with maintenance of the dose during the trial. Atomoxetine and pemoline use was excluded in this trial.

All other psychotropic medications (including antidepressants, anti-anxiety agents) were prohibited.

6.1.4.4 Adjunctive medication use

Subjects were permitted to take either lorazepam (4mg for the first week, 2mg for the second week) for control of severe agitation or zolpidem (5-10mg) for insomnia during the first 14 days of the study drug administration. Adjunctive medication use was not to be administered within 8 hours of ratings and raters were to take into account the use of adjunctive medication use. An *a priori* maximum of three days per week was established for adjunctive medication use. The table below summarizes the use of lorazepam and zolpidem during the trial.

Summary of Adjunctive Medication use During the 1st Fourteen Days

Medication Used	Placebo N=70	Depakote ER N=74
None*	58 (83%)	70 (95%)
Lorazepam	6 (9%)	4 (5%)
Zolpidem	4 (6%)	0
Both Medications	2 (3%)	0

*** p=0.033, two-tailed test with alpha set at 0.05**

When adjunctively administered, lorazepam was used for a mean 3.4 days $\pm$ 4.4 in placebo patients compared to 2.5 days $\pm$ 1.3 in Depakote ER treated patients.

More placebo patients did take adjunctive medications for the 1st 14 days which is reflective in the statistically significant difference seen between non-adjunctive using patients in the two groups. However since the vast majority of placebo patients did not use adjunctive medications (83%), it is unlikely that either the number of placebo patients that used adjunctive medication or the amount of lorazepam use in placebo patients would have substantially contributed to the ineffectiveness of Depakote ER® seen in this trial in this reviewers' assessment.

6.1.5 Efficacy Findings

Subject Disposition
Out of 229 patients screened, 151 were randomized with 150 taking at least one dose of valproic acid or placebo (ITT population).

As seen below, the completion rates were 82% for placebo vs. 74% for Depakote ER®

TABLE 3: Study M01-342 Completion rates

	PLACEBO	**DEPAKOTE ER®**
# Randomized	74	77
# treated	74	76
Total # of early discontinuations	13 (18%)	20 (26%)
Reason for Discontinuation		
Adverse event	3 (4%)	4 (5%)
Withdrew Consent	2 (3%)	3 (4%)
Lost to Follow up	3 (4%)	2 (3%)
Non compliance	1 (1%)	2 (3%)
Ineffectiveness	5 (7%)	8 (11%)
Other*	0	1 (1%)
Total	14	20

* premature discontinuation due to unspecified randomization reasons.

Protocol Deviations
There were eighteen (18) documented protocol deviations (9 each for each treatment group), which represents 12% of the randomized study population. Nine patients [five (5) placebo, four (4) Depakote] failed to meet all inclusion/exclusion criteria upon study entry as follows:

- The study blind was broken for two (2) placebo subjects
- One (1) Depakote subject had a documented lab error.
- One patient was administered a dose of 45.5mg/kg which exceeded the maximum dose of 35mg/kg.

- There were five patients who took prohibited medications during the study (two (2) placebo patients took alprazolam and clonidine; three (3) Depakote patients took clonidine, Benadryl and atomoxetine respectively).

In this reviewers' assessment, these protocol deviations are unlikely to have substantially affected the study results.

Baseline Demographics
As seen in the table below, the majority of the patients in this study were adolescent, white males.

Table 4: Demographic Characteristics of Study M01-342

DEMOGRAPHIC VARIABLE	**PLACEBO N= 70**	**DEPAKOTE N= 74**
Male (%)	43 (61%)	44 (59%)
White (%)	52 (74%)	55 (74%)
Black (%)	14 (20%)	15 (20%)
Mean Age (years)	12.8 $\pm$ 2.20	12.9 $\pm$ 2.28
Mean Weight (kg)	54.6 $\pm$ 19.36	55.3 $\pm$ 19.38

Psychiatric history/Substance Abuse history

Both placebo and Depakote ER® groups had similar Bipolar I presentations based on DSM-IV criteria, with approximately 15% experiencing their first manic episode at the time of screening. Those patients presenting with psychotic features represented 11% of the total population. Roughly 50% of the manic presentations were mixed.

Table 5: Characteristics of the Presenting DSM-IV Bipolar Diagnosis

DSM-IV BIPOLAR I DISORDER DIAGNOSIS	**PLACEBO N=70**	DEPAKOTE ER® **N=74**
Manic Episode	40 (57%)	36 (49%)
Mixed Episode	30 (43%)	38 (51%)
First Manic Episode	12 (17%)	10 (14%)
Psychotic Features	8 (11%)	8 (11%)

The majority of patients in both placebo or Depakote groups had never been hospitalized for bipolar disorder [78% (54/69) vs. 88% (65/74) respectively] or had attempted suicide [87% (59/68) vs. 92% (68/74) respectively].

A total of 11% (16/150) of randomized subjects were tobacco users and 7% (11/150) were also users of alcohol. An additional 6% (3% each for tobacco and alcohol) were classified as ex-tobacco or alcohol users in this trial. The sponsor did not provide an analysis regarding the use of substances (current or past) for the study population for this study. A review of the screening urine drug screen results revealed 3.3% (5/150) of randomized subjects in this trial tested positive for cannabinoids.

Consistent with evidenced-based literature, more than 75% of randomized patients had one or more co-morbid diagnosis, with 67% of patients meeting criteria for ADHD, with Oppositional Defiant Disorder recorded in 36% of the total population.

Table 6: History of Psychiatric Conditions by treatment group and total Randomized Population

DIAGNOSIS	**PLACEBO N=74**	DEPAKOTE ER® **N=76**	**TOTAL N=150**
ADHD	51 (69%)	49 (64%)	100 (67%)
Conduct Disorder	7 (9%)	9 (12%)	16 (11%)
Depression	14 (19%)	13 (17%)	27 (18%)
Obsessive Compulsive Disorder	2 (3%)	1 (1%)	3 (2%)
Oppositional Defiant Disorder	24 (32%)	30 (39%)	54 (35%)
Panic Disorder	2 (3%)	1 (1%)	3 (2%)

Overall the total scores for both the placebo and Depakote ER® patients at baseline on the ADHD-RS-IV home version (37 vs. 33.8 respectively) in Table 9 below suggests that both treatment groups had significant ADHD symptoms at the start of trial.

Placebo subjects were more inattentive than Depakote ER® patients at baseline as measured by the ADHD RS-IV home scale as seen in Table 7. There was also a trend in worse scores for total ADHD symptoms seen in the placebo patients vs. control at baseline, although statistical significance was not quite achieved.

Table 7: Mean Baseline Scores for ADHD-RS-IV (home version) rating scale by treatment group (ITT population)

VARIABLE	**PLACEBO N=70**	DEPAKOTE ER® **N=74**	**P-VALUE***
Inattention $\pm$ SD	20.4 $\pm$6.01	17.8 $\pm$6.52	0.013
Hyperactivity/Impulsivity $\pm$ SD	17.4 $\pm$6.60	16.0 $\pm$ 7.33	0.245
Total Score $\pm$SD	37.8 $\pm$11.36	33.8 $\pm$ 13.02	0.053

* two-tailed test, alpha=0.05

Mild depressive symptoms were present at baseline with no group differences seen in the intent-to-treat population as seen in Table 8 below.

Table 8: Summary of Baseline scores for Children's Depression Rating Scale-Revised (CDRS-R) for the ITT population

MEASURE	**PLACEBO N=70**	DEPAKOTE ER® **N=74**
Mean ± SD	35.8 ±12.87	37.1 ±12.72
Range Scores	17 to 81	19 to 71

Dosing

Patients in the Depakote ER® group attained a mean maximum daily dose of 1457mg ± 533mg (27.1 ± 6.3 mg/kg/day) with a mean modal daily dose of Depakote ER® of 1286mg ± 529mg (24.3 ± 8.0 mg/kg/day). Mean serum valproate concentrations demonstrate that the average valproate serum level resided at the lowest end of the pre-specified therapeutic concentration range both at day 28 in patients that completed 28 days of treatment, and at the final visit in the ITT population. A post-hoc analysis to examine the relationship between serum valproate concentration and change from baseline scores on the YMRS was not reported by the sponsor.

Table 9: Valproate Concentration at each Visit for Observed Cases and at final visit for all Depakote ER® **Treated subjects**

	DAY 7 (N=71)	**DAY 14 (N=67)**	**DAY 28 (N=59)**	**FINAL VISIT (N=74)**
Serum Valproate Concentration (mcg/ml) ± SD	77.3 ± 33.6	90.6 ± 40.9	82.2 ± 44.0	79.9 ± 43.7
Min-max (mcg/ml)	0-145.0	0-164.0	0-168.0	0-168.0

Overall 85% (128/150) of the patients were compliant with the study medications. Compliance was defined by the sponsor in this study as taking at least 70% of the prescribed medication.

Efficacy Results
Results from the primary endpoint efficacy analysis **failed** to show a statistically significant change in YMRS scores between placebo and Depakote ER® treated patients at the final evaluation (LOCF) or at any time point during the study.

Table 10 : Results For Mean Change From Baseline to Each visit for the YMRS (YMRS)

DAY OF MEASUREMENT	**PLACEBO**	DEPAKOTE ER®	**P-VALUE***
Baseline (SD)	31.3 (7.47) N=70	31.1 (6.78) N=74	0.716
Change to day 7 (SD)	-5.0 (7.11) N= 67	-6.0 (7.89) N=73	0.253
Change to day 14 (SD)	-6.4 (8.35) N= 70	-7.7 (8.32) N= 74	0.200
Change to day 21 (SD)	-8.3 (9.36) N= 70	-8.7 (9.42) N= 74	0.542
Change to Day 28 (SD)	-8.0 (10.56) N=70	-8.5 (8.84) N=74	0.548

* Two-way ANCOVA with an alpha=0.05, baseline value covariate with treatment and investigator as factors.
- ITT dataset used with LOCF used for dropouts

A lack of efficacy was also demonstrated on all secondary measures of efficacy as well.

6.1.6 Clinical Microbiology

Clinical microbiology data is not applicable to this clinical study.

6.1.7 Efficacy Conclusions

Efficacy was not established for Depakote ER® in the treatment of mixed phenotype adolescent mania in bipolar I disorder as defined and conducted under this single, double blind flexible dose study.

Despite the lack of efficacy seen for this particular study, one cannot definitely conclude an overall lack of efficacy for Depakote ER® in the treatment of mixed phenotype adolescent mania since clinical controversy remains over the phenotypic presentations of

bipolar mania in children and adolescents. One recent study[1] of 377 hospitalized adult bipolar patients randomized 1:1 to either Depakote ER® or placebo for 21 days (15 days of study treatment while inpatient) showed statistically significant improvement in YMRS scores in Depakote ER® treated patients vs. placebo patients starting at day 5 with continued separation throughout the study despite a large drop out rate for both groups (58% valproic acid vs. 52% PBO). Baseline YMRS scores were identical between groups and similar to the baseline YMRS values seen in the reviewed mania study above. This suggests that perhaps efficacy for Depakote ER® may be realized in hospitalized adolescent bipolar patients and/or adolescent patients with a classic adult mania phenotype presentation [distinct period (i.e. *episodic periods*) of abnormally and persistently elevated, expansive or irritable mood with associated symptoms] compared to the outpatient, mixed phenotype adolescent bipolar population that was selected for the placebo controlled study.

The continued use of stimulant medication for clinically stable co-morbid ADHD patients was a confounding factor in this study. Although reports have demonstrated significant improvement of ADHD symptoms with stimulants with no worsening of mania symptoms in pediatric bipolar patients with co-morbid ADHD after mania symptoms were successfully treated[2,3], there is no data to determine what effect un-opposed stimulant treatment in pediatric bipolar patients with co morbid ADHD would have on mood symptoms or mood stabilizer efficacy after initiation or re-institution of a mood stabilizer. As significant, objectively determined ADHD symptoms were present at baseline despite continued stimulant treatment in approximately 25% of patients with 67% meeting diagnostic criteria for ADHD, it is recommended that future pediatric bipolar studies exclude concomitant ADHD medication use during trials and limit baseline ADHD symptom severity via objectively defined measures *a priori* prior to subject randomization until data is available on un-opposed stimulant treatment for ADHD symptom control in pediatric bipolar patients.

Finally although the mean modal doses used in this study were within the pre-specified range of doses selected, the mean serum valproate concentration obtained in this flexible dose trial suggests that the doses used were, on average, able only to achieve the lowest level of the protocol-specified therapeutic concentration range of 80mcg/ml. When the YMRS data is inspected visually, there appears to be a trending towards significance in the Depakote ER® group compared to placebo at day 14, which also correlates with the time point at which the maximum mean serum valproate concentration was achieved. Though flexible dose studies are often preferred over fixed dose study designs for pediatric studies to limit the risk of over-exposure and adverse events in children and adolescents, the lack of fixed dose (or fixed plasma valproate ranges) explorations may have impaired the ability of this study to achieve optimal serum valproic acid levels and

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[1] Bowden Cl et al " A randomized, placebo-controlled, multicentered study of divalproex sodium extended release in the treatment of acute mania" *J clin Psychiatry 2006; 67:1501-1510*

[2] Scheffer RE et al "Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of co morbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium." *Am J Psychiatry* 2005 Jan;162(1):58-64.

[3] Findling RL et al "Methlphenidate in the treatment of children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder" *J Am Acad Child Adol. Psychiatry*,2007 Nov;46(11):1445-53.

demonstrate efficacy for a very debilitating illness. Therefore this reviewer suggests that additional fixed dose studies targeted at low, medium and high mean serum valproic acid ranges be considered to explore whether a dose-response relationship exists.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This review will focus only on the safety data and analysis that took place during the pediatric bipolar studies. For purposes of analysis, two separate analyses will be performed on the safety data: one from the double-blind study and the other focused on the combined safety data from the two open-label studies.

7.1.1 Deaths

No deaths occurred during any of the pediatric bipolar trials.

7.1.2 Other Serious Adverse Events

Serious adverse events (SAEs) were defined by the sponsor as those events that led to:

- Death
- were life threatening
- led to a congenital anomaly or hospitalization
- prolonged a hospital stay
- led to a persistent or significant disability
- a medical event that required medical or surgical intervention
- a spontaneous or elective abortion.

Placebo Controlled Study
There were three (3) serious adverse events reported:

- suicidal ideation with hospitalization in one placebo patient [1.3% (1/74)] and
- two [2.6% of those exposed (2/76)] in the Depakote treated group that are described below:

Subject 12010/[redacted], a 16 year old female with a past history of marijuana abuse, developed symptomatic hyperammonemia with disorientation on study day 8 of the trial after taking her evening dose of 1750mg of Depakote ER®/day. After being taken to the emergency room in the evening of day 8 with a negative head CT scan, EKG, liver function tests, serum ammonia level of 31 micromole/L and a serum valproic acid level of 144 mg/L, the patient was discharged home and instructed to discontinue the study medication. The patient's previous trough (21 hrs post dose) valproic acid level on day 7 was 132 mg/L.

The patient then went to work in the morning of day 9 but was transported back home at her request by the grandmother due to sedation. After waking up from a nap that

afternoon the subject was again disoriented and was taken to the hospital and admitted. Her hospital admission (day 9) serum ammonia level of 47 micromole/L quickly rose to 199 micromole/L the day after admission. After transfer to the ICU for lactulose administration and intensive clinical monitoring, her condition quickly improved with an uneventful hospital course without any further clinical sequelae. She was then discharged from the hospital two days after her ICU admission. A GI and Renal consult were requested to rule out a Urea Cycle Disorder however no additional information is available regarding the status of a possible diagnosis of a urea cycle disorder.

Subject 12601/[ ] was a 17 year old female with history of bipolar disorder and past history of self mutilation, one suicide attempt (Jul 2003), bulimia (2001) and opioid abuse (2004), who was admitted to the hospital on study day 5 (1-day post study drug administration) for an intentional overdose with acetaminophen, Vicodin and morphine. After a three (3) day ICU stabilization period, the patient was then transferred to a psychiatric facility without any further clinical sequelae.

Open Label studies
During the open label trials, there were eight (8) [2.7% of all exposed (8/292)] serious adverse events that were recorded as delineated below in the table:

TABLE 11: Serious Adverse Events from Open Label Studies

SUBJECT AGE (YR)/GENDER	**MEDDRA TERM**	**DAY OF ONSET**	**DAYS IN STUDY**	**SEVERITY**	**SPONSOR ASSIGNED RELATIONSHIP**
6- month Open label Extension study M02-555					
13/M	Hallucination	44 (9)	35	Severe	Probably not related
6-month Open Label Outpatient Study M02-645					
13/M	Suicidal Ideation	18 (3)	15	Moderate	Not related
12/F	Bipolar I disorder	33	64	Severe	Not related
12/M	Insulin dependant diabetes mellitus	32 (1)	31	Mild	Not related
15/M	Aggression	12	12	Severe	Possibly related
13/F	Suicidal ideation	107	141	Moderate	Probably not related
16/F	Sedation	77	112	Severe	Not related
15/F	Bipolar I Disorder	14	15	Severe	Probably not related

* Parenthesis indicates days relative to last dose of study drug.

In review of the narratives for the suicidal and aggression SAEs, all subjects had prior histories of aggressive and/or oppositional behavior or had made suicidal threats or attempts in the past.

All subjects who experienced an SAE above recovered without incident or clinical sequelae. A brief summary of the pertinent SAEs is presented below.

- The subject who was hospitalized for command hallucinations had discontinued the study drug 9 days prior. At study discontinuation this subject's antipsychotic medication was increased as he was noted to be more aggressive and anxious.

- The 16 year old female delineated above experienced sedation after an unauthorized self-administration of ziprasidone 40mg for anxiety and agitation.

- The two subjects with suicidal ideation delineated above had prior histories of suicidal threats prior to hospitalization, often in conjunction with severe environmental stressors present. These patients were hospitalized after attempting to self mutilate themselves (scratching in one patient, sticking pins in self for the other) with eventual resolution of the suicidal ideation.

During the review of the safety coding audit (please see section 7.2.8 for details), the two cases reported as "bipolar I disorder' in the open label studies were improperly coded on the case report forms, as both SAEs listed "suicidal threat" and an adverse event with 'bipolar I disorder' being delineated as a final diagnosis on the respective case report forms. Instead of reporting the adverse event, the "final diagnosis' term was reported as the adverse event.

After further review of both cases (in context with the other cases of suicidal ideation), both cases had histories of previous suicidal threats or behaviors and thus this reviewer believes that the current labeling for suicidal events is adequate and no further strengthening of the language is indicated at this time.

Reviewer's Assessment of SAEs
The hyperammonemia SAE associated with valproic acid use in the placebo controlled study is likely related to the study drug administration as current labeling for Depakote reports such an association, in addition to the temporal relationship to drug use and symptomatology seen in the case.

Although one cannot eliminate the possibility that valproic acid use contributed to the other SAEs that had occurred in all the mania studies, there is insufficient evidence from these cases to conclude that valproic acid was causally related to the events. Nevertheless post-marketing surveillance of such events is recommended for Depakote in the pediatric population.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Placebo Controlled Trial
Ineffectiveness and adverse events accounted for the primary and secondary causes for patient dropouts assigned to Depakote ER® in this study respectively. Overall 26% (20/76) of Depakote patients compared to 18% (13/74) of placebo patients prematurely discontinued the study as seen below:

TABLE 12: DISCONTINUATION RATES FROM PLACEBO CONTROLLED TRIAL

REASON FOR DISCONTINUATION	**PLACEBO N=74**	**DEPAKOTE ER® N=76**
Adverse Event	3 (4%)	4 (5%)
Ineffectiveness	5 (7%)	8 (11%)
Lost to follow-up	3 (4%)	2 (3%)
Withdrew consent	2 (3%)	3 (4%)
Non-compliance	1 (1%)	2 (3%)
Other	0	1 (1%)

Open Label Studies
'Withdrawal of consent' and 'lost to follow-up' were the primary and secondary reasons for discontinuation, together representing 31% (91/292) of the entire study population and 58% (91/157) of the total discontinuation rate as seen in the table below. Since case report form information is not available regarding the clinical course of patients for whom consent was withdrawn or those patients who were lost to follow-up in addition to a lack of a placebo control group, a pertinent analysis of these cases cannot be performed, thus limiting the ability to draw safety conclusions based on discontinuation rates from the open label studies.

TABLE 13: DISCONTINUATION RATES FROM OPEN LABEL TRIAL

REASON FOR DISCONTINUATION	**DEPAKOTE ER® N=292**
Adverse Event	33 (11%)
Ineffectiveness	18 (6%)
Lost to follow-up	40 (14%)
Withdrew consent	51 (17%)
Non-compliance	23 (8%)
Other	20 (7%)

7.1.3.2 Adverse events associated with dropouts

Placebo Controlled Trial

- Of the four (4) valproic acid patients that withdrew [5.2% (4/76)], two (2) of the withdrawals were also the patients who experienced an SAE. Therefore two (2) non-SAE related adverse events (migraine headaches and depression) occurred during the trial.

Open Label Studies

For patients that were enrolled in the 6 month open label extension study, 7.6% (5/66) of patients discontinued early as a result of an adverse event as follows: one (1) subject for obesity, two (2) for alopecia and one (1) each for decreased platelet count and increased ammonia level.

In the open label safety study, twenty eight (28) subjects [9.6% (28/292)] were discontinued early from the trial due to an adverse event: Seven (3%) were due to increased weight with aggression, insomnia, irritability and suicidal ideation each reporting two (<1%) subjects as being discontinued. One subject each was discontinued due to increased liver function test abnormality and syncope.

Reviewers Assessment of dropouts secondary to Adverse Events

Although one cannot eliminate the possibility that valproic acid use contributed to the non-SAEs adverse events that had occurred in the placebo controlled mania study that led to dropout, this reviewer concludes that there is insufficient information in these cases to conclude valproic acid use was causally related to the events or to warrant additional changes to the label at this time for these two adverse events.

Despite the inherent difficulty in attributing drug causality to adverse events that occur in open label studies, this reviewer concludes that there is insufficient information in these cases to conclude valproic acid use was causally related to the events or to warrant additional changes to the label at this time for the adverse events that had occurred in the open label studies that led to subject dropout.

7.1.3.3 Other significant adverse events

No other significant events were reported or seen.

7.1.4 Other Search Strategies

No other search strategies were performed by the sponsor.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events are any untoward medical occurrences (or signs and/or symptoms of such) in subjects administered a pharmaceutical product with or without a causal relationship to the treatment as determined by the investigators through a review of clinical and laboratory assessments. Symptoms were collected during on-site visits and telephone contacts from both spontaneous patient reports and responses to queries. Direct observations of patients during on-site visits by site personnel was also used to collect adverse events. All adverse events were to be followed to a satisfactory resolution.

Serious adverse events were collected from the time the subject signed the assent form until 30 days following discontinuation of the study drug administration had elapsed. For all other adverse events, adverse event reporting began at the time of study drug administration until 30 days following discontinuation of the study drug.

7.1.5.2 Appropriateness of adverse event characterization and preferred terms

Standard adverse event dictionaries were used to categorize both documented and verbatim reports of all adverse events. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The investigators' terminology (i.e. the 'verbatim' report) was preserved and made available.

A review of the coding audit conducted revealed miscoding of two adverse events reported as "bipolar I disorder" in the open label study (please see section 7.2.8 for details).

7.1.5.3 Incidence of common adverse events

Table 16 in section 7.1.5.4 below enumerates the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Depakote ER® in the placebo controlled study.

7.1.5.4 Common adverse event tables

Table 14: Adverse events occurring in 2% or more in Depakote ER® patients

SYSTEM ORGAN CLASS/PREFERRED TERM	**PLACEBO N=74**	**DEPAKOTE ER® N=76**
Gastrointestinal disorders		
Upper Abdominal Pain	1 (1%)	6 (8%)
Diarrhea	2 (3%)	2 (3%)
Dyspepsia	0	2 (3%)
Gastritis	0	4 (5%)

Nausea	1 (1%)	7 (9%)
Stomach Discomfort	1 (1%)	2 (3%)
Vomiting	6 (8%)	10 (13%)
General Disorders		
Fatigue	2 (3%)	3 (4%)
Infections and Infestations		
Gastroenteritis	1 (1%)	2 (3%)
Influenza	2 (3%)	2 (3%)
Streptococcal pharyngitis	0	3 (4%)
Sinusitis	1 (1%)	2 (3%)
Injury, poisoning and Procedural complications		
Contusion	0	2 (3%)
Investigations		
Ammonia Increased	0	4 (5%)
Weight Increased	1 (1%)	2 (3%)
Metabolism and Nutritional Disorders		
Decreased Appetite	2 (3%)	2 (3%)
Nervous System Disorders		
Headache	11 (15%)	12 (16%)
Migraine	0	2 (3%)
Sedation	9 (12%)	4 (5%)
Somnolence	1 (1%)	5 (7%)
Renal and Urinary Disorders		
Enuresis	0	2 (3%)
Skin and Subcutaneous Tissue Disorders		
Rash	1 (1%)	4 (5%)

7.1.5.5 Identifying common and drug-related adverse events

Those events that were common (>5% frequency) and drug related (frequency rate at least twice the rate of placebo) were: upper abdominal pain, gastritis, nausea, increased ammonia, somnolence and rash. These are summarized below in Table 15.

Table 15: Common, Drug-Related Adverse Experiences

ADVERSE EVENT-PREFERRED TERM	**DEPAKOTE ER® (N=76)**	**PLACEBO (N=74)**
Upper abdominal Pain	6 (7.9%)	1 (1.4%)
Gastritis	4 (5.2%)	0
Nausea	7 (9.2%)	1 (1.1%)
Increased Ammonia	4 (5.2%)	0
Somnolence	5 (6.6%)	1 (1.1%)
Rash	4 (5.2%)	1 (1.1%)

Reviewers Assessment of Common, Drug Related Adverse Events
As current labeling from the adult mania studies with valproic acid use does not label "Increased Ammonia" or "Rash" as common, drug related adverse events, this reviewer recommends that the above table be included into the revised labeling under Adverse Events-Pediatric Mania.

7.1.5.6 Additional analyses and explorations

The sponsor did not perform a gender or age safety analyses for the placebo controlled study. However the sponsor did provide a race and gender summary of the adverse events that occurred in the 6-month open label trial. This information was visually inspected however the information provided cannot be interpreted due to a lack of a placebo control group.

7.1.6 Less Common Adverse Events

This reviewer has reviewed all the submitted adverse event and safety reports from the phase 3 and open label safety studies. There were no other adverse events of significant concern noted.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine laboratory testing (with the exception of plasma ammonia level) for the placebo controlled trial occurred at screening, day 14 and day 28 or study termination. Ammonia testing and urinalysis occurred at screening and at day 28 or study termination. TSH, PT, PTT and urine drug screens were performed only at screening. Blinded valproate levels occurred at the day 7, 14 and 28 day visits. Urine pregnancy testing occurred at every study visit.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The focus of this analysis is the single double-blind, placebo controlled study.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency
Note: No laboratory data was obtained at randomization. Thus for purposes of laboratory analysis, "baseline" was interpreted as the clinical laboratory values obtained at the initial screening visit.

The mean change from baseline analysis is provided below. There was a statistically significant decrease in mean change 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.

Table 16: Mean Change from Baseline to Endpoint in Laboratory Parameters For the Placebo Controlled Study

Parameter (units)	Placebo			Depakote ER®		
	N	Mean Endpoint	Mean Change	N	Mean Endpoint	Mean Change
HEMATOLOGY						
RBC Count ($x10^{12}$/L)	67	4.59	-0.07	68	4.48	-0.14
Hemoglobin (g/L)	67	131.4	-2.2	68	130.8	-3.3
Hematocrit (%)	67	38.9	-0.006	68	38.8	-0.009
WBC Count ($x10^9$/L)*	67	6.84	0.6	67	6.01	-0.11
Neutrophils (%)	67	55.6	2.2	67	53.2	0.2
Lymphocytes (%)	67	34.3	-2.1	67	35.1	-2.1
Monocytes (%)*	67	5.83	-0.17	67	6.03	-0.26
Eosinophils (%)	67	3.96	0.07	67	3.89	-0.16
Basophils (%)	67	0.34	0.01	67	0.35	-0.02
Platelet Count ($x10^9$/L)*	67	277.5	-4.4	68	226.9	-50.4
CLINICAL CHEMISTRY						
Potassium (mmol/L)*	68	4.27	-0.12	67	4.41	0.05
Sodium (mmol/L)	68	140.96	0.04	67	141.4	0.58
BUN (mcmol/L)*	68	259.09	7.0	67	278.49	23.7
Creatinine (mcmol/L)	68	65.66	1.95	67	67.30	0.92
Glucose (mmol/L)	68	5.09	0.16	67	4.76	0.01
Total Calcium (mmol/L)	68	2.43	-0.01	67	2.36	-0.08
ALT (IU/L)*	68	15.6	0.06	67	12.03	-4.24
AST (IU/L)*	68	21.31	-0.76	67	20.54	-2.27
Alkaline Phosphatase (IU/L)	68	228.75	-4.19	67	216.49	-9.07
Total Bilirubin (mcmol/L)*	68	7.54	-0.05	67	6.30	-2.88
Total Protein (g/L)*	68	71.99	-1.59	67	69.16	-3.96
Albumin (g/L)*	68	44.79	-0.6	67	42.6	-3.09
Uric Acid (mcmol/L)*	68	259.09	7.00	67	278.49	23.70
Ammonia (mcmol/L)*	57	41.18	2.12	54	53.00	18.63

* $p<0.05$,one way ANOVA analysis ,two tailed alpha=0.05

Open label Studies

Over the 6-month course of treatment, platelet counts decreased by a mean 43,000 $\pm$ 56,000 from baseline values, however no bleeding disorders of adverse events of bleeding were noted in the trials.

For chemistry variables, both mean uric acid (29.55 $\pm$ 59.94) and ammonia levels (13.27 $\pm$ 24.76) increased from baseline values at final visit.

Reviewers Assessment of Laboratory Parameters
Current labeling for valproic acid mentions the association between elevated liver enzymes and thrombocytopenia in dose related fashion. Therefore no additional labeling changes are being recommended for these two laboratory parameters.

However the association between: 1.) valproic acid use and elevated ammonia and BUN 2.) the elucidation of hyperammonemia as a common and drug related adverse event and 3.) an SAE of hyperammonemia that occurred in the placebo-controlled study seen in these studies, is sufficient evidence for this reviewer to conclude that including data on the incidence of increased ammonia seen in this trial in the hyperammonemia section pf the label is recommended.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

An outlier analysis was not performed on the data.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Table 17 below displays the number of subjects who were recorded as having any potentially clinically significant changes in laboratory values. Values for potentially clinically significant (PCS) laboratory results are found in the Appendix. There were two (2) patients discontinued for increased ammonia: One was previously described in serious adverse events and the other case was recorded as an AE (Wilens 11505). Otherwise there were no additional clinical laboratory values that were reported to have led to study discontinuation or were deemed clinically significant by the investigator/sponsor.

Table 17: Patients with any Potentially Clinically Significant Laboratory Values

	PLACEBO		DEPAKOTE ER®	
LAB MEASURE	**Very Low**	**Very High**	**Very Low**	**Very High**
White Blood Cells	0	2	2	0
Neutrophils (%)	0	3	0	1
Eosinophils (%)	0	5	0	10
Potassium	0	1	0	1
Ammonia	0	2	0	4

In the open label studies (N=292), one (1) subject each was discontinued for the following abnormal laboratory parameters: increased ammonia, abnormal liver function tests, decreased platelet count. No additional information is available regarding these cases, however there were no reports of hospitalizations or clinical sequelae noted within the sponsor's submission.

7.1.7.4 Additional analyses and explorations

In addition to routine safety monitoring, the Written Request specified that in particular hepatotoxicity, hyperammonemia, pancreatitis, thrombocytopenia and rash be specifically monitored in both the placebo controlled and open label safety studies.

Hepatotoxicity
Liver function tests and ammonia levels were obtained at baseline and at endpoint in both the double blind-placebo controlled study and the open label studies. One subject from the open label mania study (subject 70708/[redacted]) was discontinued from the study on day 57 for an AST 2.6 times ULN and ALT of 1.4 times ULN. These values returned to normal after discontinuation of the medication. Otherwise no significant changes were seen in liver function tests were appreciated as delineated in table 18 in section *7.1.7.3.1* above or in the open label studies.

Hyperammonemia
Mean levels of serum ammonia were elevated from baseline values as delineated in section *7.1.7.3.1* above for the placebo controlled study. In the open label studies, 14/190 subjects (7%) that had normal baseline ammonia levels had at least one potentially clinically significant ammonia level (defined as >90 mcmol/L). A similar increase in ammonia levels also occurred during the migraine and partial seizure studies as well, with three subjects developing symptomatic hyper ammonia leading to SAEs (one as described above in the placebo controlled study, the remaining two occurred in the long term migraine and seizure studies).

Pancreatitis
Serum amylase levels were also measured in both placebo controlled and open label studies. There were no SAEs associated with pancreatitis or pancreatic disease, nor were there discontinuations due to elevated amylase levels. One subject (10813/Quintana) in the open label mania trial had an asymptomatic elevation of amylase on day 57 (413 u/l, ULN=170 u/l). A follow up amylase level on day 99 showed that the amylase level had normalized (Amylase=52 u/l).

One cannot conclude on the basis of this one case from the open label trial that the amylase elevation was either in part or whole due to Depakote ER® administration.

Thrombocytopenia
One subject in the open label mania trial was discontinued prematurely due to decreased platelet count. This subject (10121/Bergen) from the open label extension study M02-555 saw his baseline platelet count fall from a baseline of 156,000 to a low of 81,000 on day 64 of the open label study. He was discontinued form the study on day 69 with a platelet count of 93,000 and saw a normalization of his platelet count to 203,000 sixteen days after study drug discontinuation. There were no reported clinical sequelae. There were two other cases of low platelet count that met potentially clinically significant

values however neither of these subjects were discontinued early from the open label trials.

Thrombocytopenia is a known and labeled warning of valproic acid administration in adults. Though a decrease in platelet counts were seen in the placebo controlled study, the data from this one open label case is insufficient by itself to conclude a likely drug effect of valproic acid in this case of thrombocytopenia.

Rash
There were no SAEs associated with rash in either the open label or placebo controlled mania trials. One subject (72219/[redacted]) in the open label mania trial M03-647 was discontinued from the study on day 20 as a result of an erythematous and pruritic rash whereas two patients were discontinued from the migraine and partial seizure open label studies (one each respectively) due to macular papular rash. One case from the partial seizure study was associated with abdominal pain, vomiting, nausea and decreased appetite but normal clinical laboratory parameters. However seven (7) subjects (2% of all subjects) did report a rash during treatment with valproic acid during the open label trial (pp 113/779 of integrated safety summary).

In general valproic acid was not associated with severe dermatological toxicities with use, though mild-moderate rashes were reported and led to trial discontinuations in the open label trials.

7.1.7.5 Special assessments

No additional clinical laboratory special assessments were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

For the double blind study, ambulatory blood pressure and heart rate measurements were collected at all weekly visits. Additionally patient weight was obtained at screening, randomization and study completion with a physical examination performed at screening and at day 28.

7.1.8.2 Selection of studies and analyses for drug-control comparisons

The focus of this analysis is the single double-blind, placebo controlled study.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendency

Mean Change from Baseline on Blood pressure and pulse
There was no significant mean changes in either blood pressure or heart rate measurements. The vital sign safety endpoint is specified as the final evaluation (LOCF).

TABLE 18: MEAN CHANGE FROM BASELINE IN VITAL SIGN PARAMETERS-PLACEBO CONTROLLED STUDY

VARIABLE	**PLACEBO N=70**	**DEPAKOTE ER® N=74**
Systolic Blood Pressure (mmHg)		
Baseline mean	111.9	108.8
Mean Change to Final (SD)	0.2 (9.97)	2.3 (10.08)

DIASTOLIC BLOOD PRESSURE (MMHG)		
Baseline Mean	69.9	68.2
Mean Change to Final (SD)	1.2 (8.12)	1.0 (8.99)

PULSE (BPM)		
Baseline Mean	78.8	78.7
Mean Change to Final (SD)	3.0 (13.62)	3.4 (11.95)

Height and Weight
Patients that were assigned to Depakote ER® had a statistically significant 2.3 lbs increase in weight and 0.5 unit BMI increase as compared to placebo treated patients as shown below. There was no effect seen on height during this study.

TABLE 19: MEAN CHANGE FROM BASELINE IN WEIGHT PARAMETERS-PLACEBO CONTROLLED STUDY

*WEIGHT (LBS)**		
Measure	**Placebo N=65**	Depakote ER® **N=59**
Baseline Mean	118.8	123.9
Mean Change to Final ±SD	0.8 ± 2.69	2.3 ± 3.35

* p=0.005, two-tailed.

*BMI (KG/M^2)***		
Baseline Mean	22.4	22.2
Mean Change to Final ±SD	0.1 ±0.97	0.5 ±0.72

** p=0.027, two -tailed

Open Label Studies
There was a mean 6.5 lbs + 8.46 post-baseline increase in weight noted in the open label studies, leading to seven (7) early dropouts in the open label trials. Data from the open label study of 226 patients revealed a mean 6lbs and 0.63 unit BMI increase from baseline, with 16% of subjects reporting increased weight as an adverse event.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

An outlier analysis was not performed in the placebo controlled trial due to a lack of outlier vital sign measurements or abnormal shifts seen in both placebo and Depakote treated patients.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Overall there were few cases of potentially clinically significant vital sign values that occurred during the trial; none of which led to dropout. The table below delineates the cases that had occurred during the clinical trial. Please refer to the PCS criteria in the Appendix for cutoff values for very high and low values.

TABLE 20: POTENTIALLY CLINICALLY SIGNIFICANT VITAL SIGN OUTLIER VALUES-PLACEBO CONTROLLED STUDY

VARIABLE	*VERY LOW VALUES*		*VERY HIGH VALUES*	
	Placebo	**Depakote ER®**	**Placebo**	**Depakote ER®**
Systolic BP	0/70	0/74	0/70	1/74 (1%)
Diastolic BP	0/70	1/74 (1%)	0/70	0/74
Pulse	0/70	0/74	1/70 (1%)	1/74 (1%)

Open Label Studies
Thirteen (13) subjects had post-baseline PCS values for vital signs: high systolic blood pressure 5/258; high diastolic blood pressure 1/258; low diastolic pressure 5/258 and elevated heart rate 2/258. There were no reported dropouts or hospitalizations due to elevated vital sign parameters.

7.1.8.4 Additional analyses and explorations

There were no significant trends seen in mean change values for blood pressure and heart rate in the open label studies. However a mean increase of 3.1kg (-2.0, 18.0) was seen in the open label extension study, with one patient (10115/Bergen) discontinuing the trial due to increase weight.

For the 6 month stand alone open label trial, a mean 2.95 kg (SD 3.79) increase in weight was observed, with seven (7) subjects discontinuing the trial due to increased weight.

Reviewers Assessment of Vital Signs
With the exception of adding the 2.3 lbs weight gain noted in the placebo controlled trial to current labeling and the weight data obtained from the open label trial of 226 patients, this reviewer recommends that no additional labeling changes are indicated for changes in vital signs.

7.1.9 Electrocardiograms (ECG's)

7.1.9.1 Overview of ECG testing in the development program, including a brief review of preclinical results.

Electrocardiograms were obtained at screening and at day 28 (study completion) or premature withdrawal from the study. The sponsor did not subject the ECG results to statistical hypothesis testing nor were descriptive statistics used to summarize the results. As clinical experience with valproic acid and product labeling suggest a minimal effect on cardiac parameters in adults, an analysis of clinically significant ECG events, drop-outs secondary to cardiac causes and significant cardiac outlier analyses are more useful and informative metrics to evaluate the cardiac safety effects of valproic acid than mean change analyses between placebo and valproic acid groups.

Thus no conclusions regarding the effect of Depakote ER® on mean 'baseline' change pediatric electrocardiogram parameters can be made at this time.

7.1.9.2 Selection of studies and analyses for drug-control comparisons

The placebo controlled study data results were used as the basis for the electrocardiogram analysis.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

An analysis on mean change from baseline values for ECG data was not pre-specified in the protocol or performed post hoc by the sponsor.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

An analysis on outliers or trends in values from baseline ECG data was not pre-specified in the protocol or performed post-hoc by the sponsor.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

There were no reported patient discontinuations due to ECG abnormalities in either the placebo controlled studies or the open label studies.

There was one reported adverse event of an arrhythmia of moderate severity 3 days after the last dose of depakote in the open label trial (greenbaum/12401) and one case of abnormal EKG that was attributed to improper EKG lead placement. Neither of these two cases can easily be attributed to depakote administration and therefore no additional cardiac labeling is indicated at this time.

7.1.9.4 Additional analyses and explorations

No other additional analyses and/or explorations were performed.

7.1.10 Immunogenicity

Immunogenicity was not studied as part of the Written Request.

7.1.11 Human Carcinogenicity

Although the studies performed under the Written Request cannot fully address the potential carcinogenicity that may be associated with long term use, there is a low likelihood that Depakote ER® use is associated with tumor growth or potential as historical use of valproic acid has not yet yielded an association with tumor growth or carcinogenesis.

7.1.12 Special Safety Studies

Pursuant to the Written Request, cognitive/neuropsychiatric adverse events, movement assessments and effects on growth with use of valproic acid were specifically monitored and analyzed as part of the open label safety studies

Cognitive/neuropsychiatric adverse events
Cognitive/neuropsychiatric findings were assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) at baseline and at final visits during the open label study M03-647. The full scale and subscale results on the WASI demonstrates that overall valproic acid administration did not impair cognitive, verbal and performance measures during administration as evidenced by the slight mean change improvement in all scores. However some subjects showed clinically significant changes on the WASI.

Interpretation of this data is limited by the open label design of the study and thus should not be included in labeling

TABLE 21: Mean Change from Baseline to Final Evaluation for WASI scores (N=129)

WASI SUBSET TERM	**BASELINE MEAN (MIN,MAX) ± SD**	**FINAL SCORE (MIN,MAX) ± SD**	**MEAN CHANGE (MIN,MAX) ± SD**
Full Scale IQ	100.2 (60,147) ± 16.22	103.4 (56,138) ± 16.48	3.2 (-34,31) ± 8.52
Verbal Scale IQ	101.2 (44,152) ± 18.05	104.3 (59,149) ± 18.87	3.0 (-40,46) ± 10.31
Performance Scale IQ	98.4 (46,131) ± 15.43	102 (60,132) ± 13.61	3.6 (-23,25) ± 7.39
Subset T- Scores			
Vocabulary	50.3 (20,77) ± 11.53	51.8 (20,76) ± 12.62	1.4 (-25,23) ±7.10

Matrix Reasoning	48.8 (20,67) ± 10.77	51.2 (20,68) ± 9.09	2.4 (-14,27) ± 6.98
Similarities	50.4 (21,80) ± 11.87	52.1 (23,79) ± 11.97	1.7 (-24,30) ± 7.57
Block Design	101.2 (24,80) ± 11.87	104.3 (24,79) ± 11.97	3.0 (-21,30) ± 7.57

Behavior assessments

Behavior assessments with valproic acid use were performed at baseline and at final study visit in the open label study M03-647 using the parent administered Behavior Assessment System for Children (BASC). Depakote ER® administration led to slight improvements in various behaviors as seen in the table below adapted from the submitted NDA.

Interpretation of this data is limited by the open label design of the study and thus should not be included in labeling.

Table 22: Summary of mean change from baseline to final values for BASC age specific T-scores

VARIABLE	***AGES 10-11 (N=20)***		***AGES 12-18 (N=114)***	
	Baseline Mean T-Score	**Mean Change (SD) to Final**	**Baseline Mean T-Score**	**Mean Change (SD) to Final**
Hyperactivity	75.8	-13.9 (16.69)	79.5	-11.0 (17.80)
Aggression	75.7	-11.8 (13.00)	72.6	-7.4 (12.58)
Conduct Problems	76.5	-10.1 (16.26)	79.5	-7.5 (15.59)
Anxiety	57.3	-4.1 (11.47)	64.5	-5.4 (13.30)
Depression	83.2	-14.7 (14.05)	73.4	-9.9 (16.60)
Somatization	56.2	-2.9 (8.81)	58.9	-3.6 (14.14)
Atypicality	73.7	-9.6 (17.76)	68.2	-7.0 (16.96)
Withdrawal	54.4	-3.6 (6.48)	60.7	-3.7 (13.73)
Attention Problems	71.1	-6.3 (5.59)	71.7	-3.6 (11.27)
Adaptability	28.8	4.2 (6.23)		
Social Skills	35.9	4.4 (6.78)	35.2	2.2 (8.51)
Leadership	40.6	0.4 (6.34)	40.1	-0.7 (7.24)

Note: For adaptability, social skills and leadership, higher scores reflect improved functioning. Otherwise lower scores represent improved functioning.

Movement assessments

As per the Written Request, abnormal movement assessments were assessed using the UKU Side Effects Rating scale in study M03-647 at baseline, every month for the first three months and at month 6. Results show that 7% of patients demonstrated at least one neurological side effect at baseline with 4% of patients at month 6 demonstrating a neurological side effect. Of note, only 100 patients from the original 219 patients at baseline (~46%) had a month 6 assessment on the UKU rating scale, thus limiting the interpretation of any long term neurological side effects that might been seen with

valproic acid use. In addition, at least 32 patients (14% of subjects) had missing post-baseline side effect UKU ratings.

With the exception of tremor and at month 2 for hypokinesia/akinesia, there were no additional increases in rate of the measured movement effects during open label treatment with valproic acid (see table below).

Interpretation of this data is limited by the open label design of the study and thus should not be included in labeling.

TABLE 23: NUMBER AND PERCENTAGES OF UKU SIDE EFFECTS PER TIME POINT

UKU Side Effect Term	Baseline (N=219)	Month 1 (N=192)	Month 2 (N=165)	Month 3 (N=152)	Month 6 (N=100)
Any Neurological Side Effect	15 (7%)	11 (6%)	9 (5%)	4 (3%)	4 (4%)
Dystonia	1 (<1%)	1 (<1%)	1 (<1%)	0	0
Rigidity	1 (<1%)	0	0	0	0
Hypokinesia/Akinesia	1 (<1%)	1 (<1%)	2 (1%)	0	0
Hyperkinesia	9 (4%)	4 (2%)	5 (3%)	0	1 (1%)
Tremor	5 (2%)	4 (2%)	2 (1%)	4 (3%)	3 (3%)
Akathesia	7 (3%)	4 (2%)	2 (1%)	0	0

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No new information was presented as part of this submission that was relevant to the abuse potential of Depakote ER®. Since valproic acid is neither a controlled nor scheduled substance per the Drug Enforcement Agency (DEA), the abuse potential of valproic acid is likely to be very low.

An optional two week taper period was available to patients at the conclusion of the open label study M03-647. In addition, those subjects who developed an adverse event after the last dose of study medication or who developed increases in severity of an adverse event at the conclusion of the study were monitored. Thirteen (13) of 226 patients elected to undergo a taper period, of which three (3) of the thirteen subjects had an adverse event that began after the open label period. Two of the adverse events recorded for one patient were nausea, stomach ache, diarrhea and vomiting 5 days after taking the study medication. The investigator interpreted this case as a drug withdrawal syndrome. In this particular case, the symptoms lasted 9 days without any clinical intervention without any clinical sequelae noted by the sponsor. Another subject, a 13 year old male, developed suprapubic pain after discontinuation from the study after only 2 doses of study medication. Although this was reported as drug related, it is unlikely related to withdrawal or a rebound effect of the study drug administration after two doses of study drug administration was given.

7.1.14 Human Reproduction and Pregnancy Data

No subjects became pregnant during their participation in the mania studies. However eight (8) subjects did become pregnant under the migraine prophylaxis studies. The reader is referred to the review of these cases as part of the NDA review for the migraine prophylaxis studies for a full analysis.

7.1.15 Assessment of Effect on Growth

Height and weight parameters were measured in both the placebo controlled study at baseline and study endpoint, and at baseline, 3 months and 6 months in the open label studies. Results from the open label studies for height are presented will only be reviewed.

Height was increased in all open label studies, with a mean 1.9 $\pm$ 2.81cm increase seen in the mania studies. There was one adverse event of "increased height" reported in the open label trial. However a z-score analysis was not performed for the open label studies.

7.1.16 Overdose Experience

In the open label mania study M03-647, a 15-year old patient took five extra Depakote ER® pills on day 55 of the study. No associated symptoms were present and no action was taken.

The current labeling has described cases of somnolence, heart block, coma and death with overdoses of valproic acid.

A review of the Agency post marketing surveillance system listed 45 Med watch reports of Depakote overdoses in patients 17 years of age or less. Similar to current labeling, sedation, coma, heart block, hepatic failure and thrombocytopenia was associated with Depakote overdoses in this patient population.

Based on this review, no additional information needs to be added to the overdose section of the labeling in reference to pediatric overdoses.

7.1.17 Post marketing Experience

Depakote ER® has not been marketed for patients under age 17 for bipolar disorder.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Pursuant to the Written Request for studies of mania in adolescents, one hundred and fifty (150) patients were exposed to Depakote ER® or placebo for 4 weeks in a placebo controlled study with 66 of these patients participating in a 6-month open label extension safety study (26 completed entire study). An additional separate 6-month open label study of 227 patients (with 109 completing) with Depakote ER® was also performed. In total, 303 patients were exposed to flexible doses of Depakote ER® vs. 74 placebo patients during the adolescent mania program.

7.2.1.2 Demographics

Demographic data for the placebo controlled study reveals that the majority of the patients were white males with approximately 2/3rd of the patients aged 10-13 years old.

TABLE 24: DEMOGRAPHICS-PLACEBO CONTROLLED STUDY

Demographic Characteristic	Placebo N = 70	Depakote ER N = 74	Total N = 144	p-value[a]
Gender				0.865
Female	27 (39%)	30 (41%)	57 (40%)	
Male	43 (61%)	44 (59%)	87 (60%)	
Race				> 0.999
White	52 (74%)	55 (74%)	107 (74%)	
Black	14 (20%)	15 (20%)	29 (20%)	
American Indian/ Alaska Native/White	1 (1%)	0 (0%)	1 (< 1%)	
Asian/White	0 (0%)	1 (1%)	1 (< 1%)	
Black/White/Other	0 (0%)	1 (1%)	1 (< 1%)	
Other[b]	3 (4%)	2 (3%)	5 (3%)	
Hispanic				0.391
Yes	8 (11%)	5 (7%)	13 (9%)	
No	62 (89%)	69 (93%)	131 (91%)	
Age (years)				0.921
Mean (SD)	12.8 (2.20)	12.9 (2.28)	12.8 (2.23)	
Range	10 - 17	10 - 17	10 - 17	
Age Distribution				0.727
10 to 13 years	47 (67%)	47 (64%)	94 (65%)	
14 to 17 years	23 (33%)	27 (36%)	50 (35%)	
Height (cm)				0.411
Mean (SD)	154.2 (12.90)	156.0 (13.23)	155.2 (13.06)	
Range	130.0 - 188.0	127.0 - 188.0	127.0 - 188.0	
Weight (kg)				0.817
Mean (SD)	54.6 (19.36)	55.3 (19.52)	55.0 (19.38)	
Range	27.0 - 99.0	30.0 - 105.0	27.0 - 105.0	
BMI (kg/m^2)				0.823
Mean (SD)	22.4 (5.65)	22.2 (5.43)	22.3 (5.52)	
Range	14.3 - 37.0	14.8 - 39.6	14.3 - 39.6	

SD = standard deviation

a. p-values are from Fisher's exact test (gender, race, Hispanic, and age group) or a one-way ANOVA (age, height, weight, and BMI). Races other than white were combined for calculation of p-values.

b. Includes two (2) Hispanic, one (1) Amerasian, one (1) Bi-racial White + Black and one (1) Jewish subject.

7.2.1.3 Extent of exposure (dose/duration)

For the placebo controlled trial, the mean duration of drug exposure was similar between placebo (25.5 days ± 6.6) vs. valproic acid (24.3 days ± 7.1). A mean daily dose of 1457.2 ± 532.9 mg/day (range 750-3250mg) or 27.1 ± 6.3 mg/kg/day was achieved in the valproic acid group. The mean modal dose was slightly lower than the mean daily dose (1286.2 ± 528.7 mg/day), however this is not likely a significant decrease to affect the study results since both doses are considered to be in the recommended daily therapeutic range for valproic acid based on a mg/kg/basis.

During the open label mania studies, total subject exposure to Depakote ER® was 98.1 patient years with a final mean valproic acid level of 70.8 ± 39.8 achieved. A mean daily dose of 1328.8 ± 559.4 mg with a mean modal daily dose of 1187.5 ± 554.3 mg was achieved with a mean duration of 122.7 ± 66.4 days. On a mg/kg basis, the mean dose achieved was 23.5 ± 8.6 mg/kg/day of valproic acid with a mean modal dose of 21.0 ± 8.3 mg/kg/day.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

All the submitted efficacy and safety data that is being used has been derived from the Depakote ER® pediatric mania clinical program and is contained within the NDA submission. There are no secondary sources of safety and/or efficacy data that were submitted or have been mentioned by the sponsor with this submission.

Additional studies for a pediatric migraine prophylaxis and partial seizure disorder indication were also performed under the Written Request and were submitted under NDA 21-168. The reader is referred to this NDA for further analyses on these studies.

7.2.2.2 Post marketing experience

The post marketing experience with valproic acid in children and adolescents with bipolar disorder has not been systematically tracked as its use in the pediatric bipolar population has not been Agency approved. However post marketing safety reports have been reviewed in this population and were included as part of the corresponding supplement NDA 21-168.

7.2.2.3 Literature

The sponsor conducted a literature search and analysis in support of a labeling change to include pediatric pharmacokinetic dosing guidelines. Please refer to section 5.1 for details on this literature search.

7.2.3 Adequacy of Overall Clinical Experience

The clinical studies submitted are adequate to fulfill the requirements pursuant to the Written Request.

Considerable debate remains in the field of child psychiatry over the phenotypic presentation of pediatric bipolar disorder. This debate has centered around the interpretation of the DSM-IV criteria for mania and has led to essentially two different interpretations: a broad interpretation of the DSM-IV criteria leading to the 'broad phenotype' presentation of mania and a narrow interpretation of the DSM-IV criteria consequently that has given rise to a 'narrow phenotype' presentation of mania in pediatric bipolar disorder.

In general terms, the broad interpretation has proposed that mania, as defined in Criteria A of the DSM-IV, can be established if there is a distinct period of abnormally and persistently elevated, expansive, **OR** irritable mood, lasting at least one week. This has led some child psychiatry researchers to purport that the broad phenotypic presentation is characterized by severe irritability and that severe irritability alone is only needed to satisfy Criteria A for diagnostic purposes and thus periods of severe irritability and/or mood swings can be considered a manic episode.

In contrast, since irritability has generally been a non-specific symptom and finding in child psychiatry and the DSM-IV (irritability is seen in pediatric depression, ADHD, anxiety, oppositional defiant disorder among other diagnoses), a more conservative and traditional 'narrow' interpretation of the DSM-IV criteria has been proposed by other psychiatric researchers[4]. With this interpretation, distinct periods (i.e. distinct episodes) of abnormally and persistently elevated/expansive mood (Criteria A) and/or Grandiosity (Criteria B) must be evident to warrant a mania diagnosis. Clinically, the 'narrow' phenotypic presentation of pediatric bipolar disorder is phenomenologically similar to the typical presentation of bipolar seen in adults.

Despite the controversy, there is insufficient longitudinal evidence at present on both phenotypes to determine which phenotypic presentation will lead to an adult bipolar diagnosis. However recent data has been published which has demonstrated that certain executive functioning deficits are present in a higher rate in first order relatives with bipolar disorder of narrow phenotype bipolar patients and that parents of children with narrow phenotype bipolar disorder are significantly more likely to be diagnosed with bipolar themselves.[5] Faced with this knowledge, one cannot conclude lack of valproic efficacy for 'pediatric bipolar' disorder until adequate, placebo controlled studies in both phenotypes are conducted.

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[4] Leibenluft EL et al "Defining clinical phenotypes of juvenile mania" *Am J Psychiatry* 2003 Mar;160(3):430-7

[5] Brotman MA "Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation". *Am J Psychiatry* 2007 Aug;164(8):1238-41.

As delineated previously, the choice of using a flexible dose design and the concomitant use of stimulant medication (un-opposed at randomization) are significant confounding factors that may have contributed to the lack of efficacy demonstrated in this study.

Thus until adequately dosed, placebo-controlled trials of valproic acid in both narrow and broad phenotype presentations of pediatric bipolar disorder becomes available, this reviewer has insufficient data to definitively conclude at this time that efficacy for pediatric mania does not exist for valproic acid.

7.2.4 Adequacy of Special Animal and/or *In vitro* Testing

No animal or *in vitro* testing studies were performed or required as part of the Written Request. In addition, the current labeling for Depakote ER® has information from previous preclinical and *in vitro* testing of valproic acid included.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No formal metabolic, clearance or drug interaction data or information was required or performed pursuant to the Written Request. In addition, this information is currently available as part of the current labeling for valproic acid.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The pediatric studies conducted under this NDA were adequate to evaluate pediatric adverse events associated with Depakote ER® use. No further study recommendations for pediatric adverse event monitoring are indicated at this time as there is insufficient data to recommend Depakote ER® for the treatment of pediatric mania.

7.2.8 Assessment of Quality and Completeness of Data

Review of case report forms, narrative and adverse event line listings for each of the patients listed below in Table 26 was conducted. Consistent reporting was noted in adverse events between all three databases with no errors noted for studies M01-342 and M02-555.

A review of the case report form from M03-647 [redacted]71704 revealed that the adverse event description was recorded as “suicidal threat” with a final diagnosis of “bipolar I disorder” also recorded. In reporting the adverse event, the information recorded in the “Final diagnosis/syndrome” box was reported as the adverse event rather than the event description. Further review from study M03-647 revealed a second MedDRA preferred

term “Bipolar I Disorder” recorded for [redacted]/70701. Review of this CRF revealed that the adverse event description was recorded as “suicidal and homicidal threat” with a final diagnosis of “Bipolar I disorder” being recorded and reported as the MedDRA preferred adverse event term. Both patients were hospitalized without incident and with no reported clinical sequelae.

Reviewing other CRF’s from study M03-647 reveals that the information recorded in the Event Description section of the CRF were used to generate the MedDRA preferred term database rather than the terms found in the Final Diagnosis section of the form.

TABLE 25: DEPAKOTE ER® CRF AUDIT

PID (UNIQUE ID)	CASE REPORT FORM AE’S	NARRATIVE SUMMARY	JMP AE LISTING
M01-342 Martinez/Wagner/11401	Swelling Face, Rash Maculopapular	OK	OK
M01-342 Sendi/12601	Intentional Overdose	OK	OK
M01-342 Simkin/12010	Disorientation, Ammonia Increased	OK	OK
M02-555 Bergen/10107	Hallucination/Hospitalization	OK	OK
M02-555 Bergen/10121	Platelet count decreased	OK	OK
M03-647 [redacted]/70615	Suicidal ideation/Hospitalization	OK	OK
M03-647 [redacted]70904	Aggression/Hospitalization	OK	OK
M03-647 [redacted]/71704	Suicidal Thoughts/hospitalization	NO	NO

7.2.9 Additional Submissions, Including Safety Update

No additional submissions were required or performed pursuant to the Written Request.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Safety data only from the placebo controlled study was reviewed to determine mean change from baseline differences in laboratory and vital sign data for Depakote ER®. The safety data from the open label studies M02-555 and M03-647 were pooled and reviewed in response to the specific additional long term safety requirement as delineated in the Written Request.

Efficacy data was only reviewed from the placebo controlled, double blind study.

7.4.1.2 Combining data

Safety data from the two open label studies were combined with an analysis performed via a separate Integrated Safety Study.

Although the diagnostic screening instruments used between the two studies differed slightly, this reviewer feels that the differences are not severe enough to prohibit pooling of the safety data from these two studies.

7.4.2 Exploration for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Due to the flexible dose study design form the placebo controlled study, an analysis of dose related adverse events cannot be performed.

7.4.2.2 Explorations for time dependency for adverse findings

Time dependent studies were not performed as there were no long term controlled data that was collected during the clinical development program.

7.4.2.3 Explorations for drug-demographic interactions

Please see section 7.1.5.6 for additional analysis.

7.4.2.4 Explorations for drug-disease interactions

No additional studies were performed in patients with clinically significant medical illnesses.

7.4.2.5 Explorations for drug-drug interactions

There were no explorations done to examine drug-drug interactions in the clinical development program.

7.4.3 Causality Determination

In this review, causality was determined if an adverse event occurred in 5% or greater of patients taking Depakote ER® compared to placebo AND that the adverse event reporting rate in patients taking drug was at least twice the rate in placebo patients.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

A combined clinical/objective strategy was employed in the pediatric efficacy study whereby the initial dose based on weight was flexibly adjusted on the basis of both clinical response and plasma drug levels.

8.2 Drug-Drug Interactions

There are no further recommendations at this time for dose adjustments for Depakote ER® in pediatric patients taking concomitant medications.

8.3 Special Populations

8.4 Pediatrics

The clinical development program was conducted pursuant to the Agency's Written Request with Pediatric Exclusivity granted by the Agency on December 12, 2007.

8.5 Advisory Committee Meeting

Not applicable at this time.

8.6 Literature Review

Relevant reviews of the literature that are pertinent to this review have been cited throughout the review and in the references section of this NDA.

8.7 Post marketing Risk Management Plan

Not applicable at this time.

8.8 Other Relevant Materials

Please refer to section 3 for reviews from other disciplines.

9 OVERALL ASSESSMENT

9.1 Conclusions

Overall the submitted studies under this NDA met the terms of Written Request despite a lack of efficacy seen. Despite the diagnostic controversies surrounding pediatric bipolar disorder and the limitations and confounding factors present in this study, these studies have contributed significantly to the limited body of knowledge on valproic acid treatment and safety issues in pediatric bipolar disorder. It is often more clinically useful

to know that clinically used treatments based on empirical evidence actually fail to demonstrate efficacy that to continue to subject patients to unwarranted adverse effects that may have very little benefit. Though it is premature at this time to decree a total lack of efficacy of valproic acid in the treatment of pediatric bipolar disorder, the results of this study nevertheless serve as an evidence based foundation for clinical use and development of future clinical research for valproic acid in this population.

Additional clinical monitoring for ammonia, along with weight gain are significant safety issues are important facts associated with pediatric use of valproic acid that warrant inclusion in clinical labeling.

9.2 Recommendations on Regulatory Action

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, neither an approval/approvable nor a non-approval action is indicated for this NDA submission.

9.3 Recommendations on Post marketing Actions

Please see section 1.2

9.3.1 Risk Management Activity

Please see section 1.3.

9.3.2 Required Phase 4 Commitments

This reviewer recommends no additional Phase 4 requirements at this time.

9.3.3 Other Phase 4 Requests

Not applicable.

9.4 Labeling Review

Please refer to section 10.2 for a full line by line labeling review and labeling recommendations.

9.5 Comments to Applicant

Please see section 1.2

10 APPENDICES

Appendix 1. Potentially Clinically Significant (PCS) Criteria for Laboratory and Vital Signs Values in Children and Adolescents

	Very Low		Very High	
Hematology	**Domestic Units**	**International Units**	**Domestic Units**	**International Units**
Hemoglobin 3-12 years old > 12 years old	≤ 9 g/dL ≤ 10 g/dL	≤ 90 g/L ≤ 100 g/L	≥ 19 g/dL ≥ 19 g/dL	≥ 190 g/L ≥ 190 g/L
Hematocrit	≤ 28%	≤ 0.28 (fraction)	≥ 55%	≥ 0.55 (fraction)
Red Blood Cells	$\leq 3.0 \times 10^{12}$/L	$\leq 3.0 \times 10^{12}$/L	$\geq 6.5 \times 10^{12}$/L	$\geq 6.5 \times 10^{12}$/L
White Blood Cells	$\leq 3.0 \times 10^{9}$/L	$\leq 3.0 \times 10^{9}$/L	$\geq 17.0 \times 10^{9}$/L	$\geq 17.0 \times 10^{9}$/L
Platelet Count	$\leq 110 \times 10^{9}$/L	$\leq 110 \times 10^{9}$/L	$\geq 600 \times 10^{9}$/L	$\geq 600 \times 10^{9}$/L
Eosinophils	No criterion	No criterion	≥ 8%	≥ 8%
Basophils	No criterion	No criterion	≥ 5%	≥ 5%
Lymphocytes	≤ 1%	≤ 1%	≥ 70%	≥ 70%
Monocytes	≤ 0.12%	≤ 0.12%	≥ 15%	≥ 15%
Neutrophils 3-5 years old 6-17 years old	≤ 10% ≤ 20%	≤ 10% ≤ 20%	≥ 60% ≥ 80%	≥ 60% ≥ 80%

Chemistry	Very Low		Very High	
	Domestic Units	International Units	Domestic Units	International Units
Albumin	≤ 2.8 g/dL	≤ 28 g/L	≥ 5.8 g/dL	≤ 58 g/L
Alkaline Phosphatase	No criterion	No criterion	≥ 3 × ULN	3 × ULN
BUN	No criterion	No criterion	≥ 30 mg/dL	≥ 10.71 mmol/L
Calcium	≤ 6 mg/dL	≤ 1.5 mmol/L	≥ 13 mg/dL	≥ 3.25 mmol/L
Cholesterol	No criterion	No criterion	≥ 300 mg/dL	≥ 7.8 mmol/L
Creatinine	No criterion	No criterion	≥ 2.0 mg/dL	≥ 176.8 mcmol/L
Total Bilirubin	No criterion	No criterion	≥ 2.0 mg/dL	≥ 34.2 mcmol/L
Glucose	≤ 45 mg/dL	≤ 2.475 mmol/L	≥ 250 mg/dL	≥ 13.75 mmol/L
Inorganic Phosphorus	≤ 2.0 mg/dL	≤ 0.646 mmol/L	≥ 6.5 mg/dL	≥ 2.0995 mmol/L
Potassium	≤ 3.0 mEq/L	≤ 3.0 mmol/L	≥ 5.8 mEq/L	≥ 5.8 mmol/L
AST	No criterion	No criterion	≥ 3 × ULN	≥ 3 × ULN
ALT	No criterion	No criterion	≥ 3 × ULN	≥ 3 × ULN
Sodium	≤ 125 mEq/L	≤ 125 mEq/L	≥ 150 mEq/L	≥ 150 mEq/L
Total Protein	≤ 5.0 g/dL	≤ 50 g/L	≥ 9.5 g/dL	≥ 95 g/L
Uric acid	No criterion	No criterion	≥ 9 mg/dL	≥ 535.32 mcmol/L
Ammonia	No criterion	No criterion	≥ 90 mcmol/L	≥ 90 mcmol/L

ULN= Upper Limit of Normal

Vital Signs (units)	Very Low (VL)	Very High (VH)
Systolic Blood Pressure (mm Hg) 3-10 years old > 10 years old	≤ 70 and decreased ≥ 20 from baseline ≤ 75 and decreased ≥ 20 from baseline	≥ 135 and increased ≥ 20 from baseline ≥ 150 and increased ≥ 20 from baseline
Diastolic Blood Pressure (mm Hg) 3-10 years old > 10 years old	≤ 40 and decreased ≥ 15 from baseline ≤ 50 and decreased ≥ 15 from baseline	≥ 90 and increased ≥ 15 from baseline ≥ 100 and increased ≥ 15 from baseline
Heart Rate (bpm) 3-10 years old > 10 years old	≤ 60 and decreased ≥ 20 from baseline ≤ 45 and decreased ≥ 20 from baseline	≥ 130 and increased ≥ 20 from baseline ≥ 120 and increased ≥ 15 from baseline

Efficacy Appendix

Table 27: Principal Investigators for Efficacy Study

Principal Investigator	Site	N-enrolled
PHASE 3 STUDY		
STUDY M01-342		
Grant Belnap, MD		

Principal Investigator	Site	N-enrolled
Deborah Bergen, MD	24051	16
Jeffrey Borenstein, MD		
Guy Brannon, MD	25071	3
Kiki Chang, MD	22942	4
David Duesenberg, MD	22943	4
Michael Greenbaum, MD	31503	3
Sanjay Gupta, MD	15479	1
Robert Hendren, DO	22946	1
Willis Holloway Jr., MD	31757	7
Gregory Kaczenski, MD	22947	1
Ali Kashfi, MD	22949	6
Alain Katic, MD		
David Krefetz, DO		
Bennett Leventhal, Jr., MD	22949	1
Melissa Martinez/Wagner, MD	32167	8
Thomas Okamoto, MD		
Sohail Punjwani, MD	26063	10
Humberto Quintana, MD	22954	12
Linda Rhodes, MD		
Robert Riesenberg, MD	6542	3
Michael Rieser, MD	22956	11
Adelaide Robb, MD	22957	7
Scott Segal, MD	26065	19
Ismail Sendi, MD, MS	20602	3
Franco Sicuro, MD	31759	3
Deborah Simkin, MD	22958	6
Thomas Shoaf, MD	30539	2
William Terry, MD	22959	17
Karen Wagner, MD,PhD		
Timothy Wilens, MD	22960	2

10.1 Review of Individual Study Reports

Please see section 7

10.2 Line-by-Line Labeling Review

This review will only focus on labeling changes related to pediatric mania and the pediatric safety data obtained from the pediatric mania studies performed under NDA 22-267.

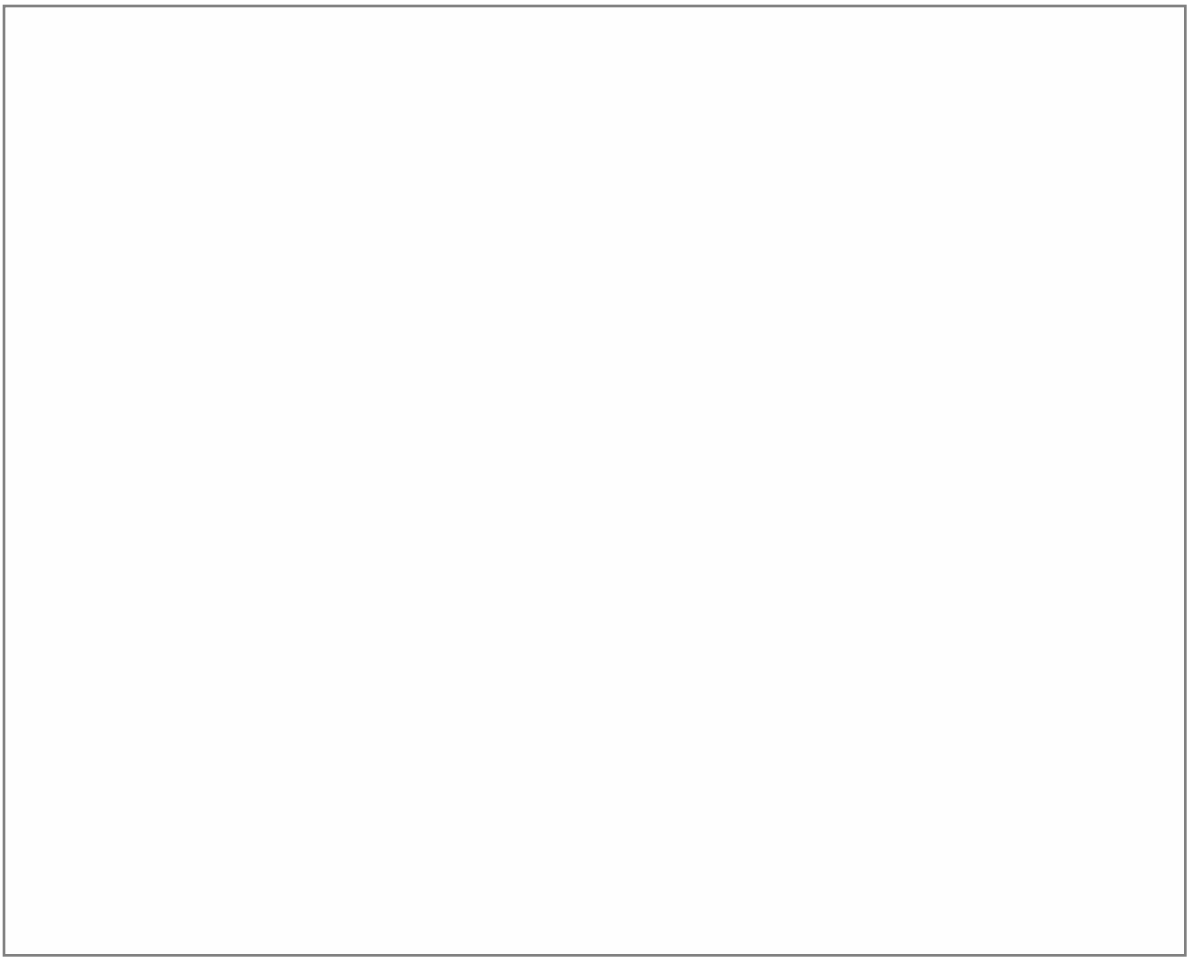
Additional pediatric labeling changes are being performed for pediatric migraine prophylaxis and partial complex seizure disorders by the Division of Neurology Products

under NDA 21-168. Please refer to this NDA and/or labeling supplements for additional information.

The sponsor has also submitted labeling changes based on the results from these NDAs in the new Physician's Labeling Rule (PLR) format. After internal discussions with the Division of Neurology products, it was determined that a recently approved PLR version of labeling for a 505 b(2) valproic acid capsule product would serve as the template for the labeling changes based on the pediatric data submitted with the NDAs. However as the 505 b(2) labeling is based on the labeling for Depakote delayed release capsules and not Depakote ER® tablets, additional labeling changes are also being recommended by this reviewer as to conform to current Depakote ER® labeling.

Therefore this review will first focus on the differences in labeling between Depakote Capsules and Depakote ER® Tablets. This is to be followed with specific changes and language to be included into the 505 b(2) PLR labeling for Depakote ER®.

I. Line by Line Review between current Depakote Capsules vs. Depakote ER® tablet non-PLR labeling.



Pages 56 through 61 redacted for the following reasons:
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REFERENCES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mark Ritter
3/4/2008 09:56:38 AM
MEDICAL OFFICER

Ni Aye Khin
3/4/2008 04:44:25 PM
MEDICAL OFFICER
See also memo to file for additional comments.