CLINICAL REVIEW

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Reviewer Name	Martin S. Rusinowitz, M.D.
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Established Name	Depakote ER Depakote Sprinkle
(Proposed) Trade Name	
Therapeutic Class	Antiepileptic, Anti-mania
Applicant	Abbott
Priority Designation	P
Formulation	
Dosing Regimen	
Indication	
Intended Population	

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1 EXECUTIVE SUMMARY

The following summary consists only of the efficacy review on migraine prophylaxis in children.

1.1 Recommendation on Regulatory Action

This Reviewer recommends that Depakote ER not be approved for migraine prophylaxis in adolescents.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Depakote ER, divalproex sodium extended release, is a compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. In adults, Depakote is indicated in the treatment of mania, migraine prophylaxis and epilepsy.

In response to the FDA's written request of January 31, 2006, pursuant to Section 505 A of the Federal Food, Drug and Cosmetic Act (that information be submitted from studies in migraine prophylaxis in an adolescent pediatric population, the objective of this study was to compare the safety and efficacy of Depakote ER to placebo in the prophylactic treatment of migraine headache in adolescents.

This study consisted of a single Phase 3, randomized, double blind, placebo controlled, parallel-group, multicenter study which included 300 randomized adolescent subjects with a history of migraine.

1.3.2 Efficacy

Study M02-488 was a Safety and Efficacy study of Divalproex Sodium Extended-Release Tablets in Migraine Prophylaxis: A Double-Blind, Placebo-Controlled Study in Adolescents.

Depakote ER did not differentiate from placebo in the prophylactic treatment of migraine.

The primary endpoint, the Experimental Phase reduction from baseline in 4-week migraine headache rate, showed no dose response effect. The data was evaluated using a one-way ANOVA of rank-transformed data.

Table 11. Experimental Phase Reduction From Baseline in 4-Week Migraine Headache Rate (Intent-to-Treat Dataset)

		Depakote ER		
Measurement	**Placebo N = 71**	**250 mg N = 81**	**500 mg N = 74**	**1000 mg N = 73**
Baseline:				
Mean (SD)	4.0 (1.31)	4.0 (1.27)	3.9 (1.28)	3.6 (1.08)
Median	4.0	4.0	4.0	3.1
Reduction from Baseline:				
Mean (SD)	1.7 (1.74)	1.6 (1.70)	1.5 (1.55)	1.5 (1.59)
Median	1.7	1.7	1.4	1.7
p-value vs. placebo[a]		0.841	0.425	0.589

As was the case for the primary efficacy variable, there were no statistically significant differences between any Depakote ER dose group and placebo for the principal secondary efficacy variables of: Experimental Phase reduction from baseline in 4-week migraine headache rate for the last four weeks of the Experimental Phase; the Experimental Phase reduction from baseline in 4-week migraine headache rate, excluding possible migraines (treated with symptomatic medication); the Experimental Phase percent reduction from baseline in 4-week migraine headache rates, assessing both actual values and the proportion of subjects with at least a 50% reduction; and the Experimental Phase reduction from baseline in the number of migraine headache days per four weeks.

1.3.3 Safety .

See safety review.

1.3.4 Dosing Regimen and Administration

The dosing regimen and administration consisted of oral dosages of Depakote ER in 250 mg, 500 mg and 1,000 mg along with a placebo.

1.3.5 Drug-Drug Interactions

None found.

1.3.6 Special Populations

This study adequately assessed the use of Depakote ER for migraine prophylaxis in the special population of adolescents with chronic migraine headaches.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Divalproex sodium is a stable compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. The drug is available in the following formulations:

Depakote DR	NDA 18-873, NDA 20-320
Depakote ER	NDA 21-168
Depakote Sprinkle capsules	NDA 19-680
Depacon injection	NDA 20-593
Depakene capsules	NDA 18-081
Depakene syrup	NDA 18-082

The product has already received FDA approval for:

- Manic episodes associated with bipolar disorder
- Prophylaxis of migraine headaches in adults
- Monotherapy and adjunctive therapy in complex partial seizures that occur either in isolation or in association with other types of seizures in adults and children 10 years of age or older.
- Use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively with multiple seizure types that include absence seizures.

2.2 Currently Available Treatment for Indications

There are no approved alternative prophylactic migraine treatments in adolescent patients.

2.3 Availability of Proposed Active Ingredient in the United States

No issue identified.

2.4 Important Issues With Pharmacologically Related Products

None identified.

2.5 Presubmission Regulatory Activity

Valproic Acid, in various formulations outlined above, has been available for almost 30 years. No issue identified.

2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

None identified.

3.2 Animal Pharmacology/Toxicology

None identified.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The review of clinical efficacy is solely based on one multicenter trial study, Protocol MO2-488.

4.2 Tables of Clinical Studies

TABLE 2.2 page 1, unless better one identified

4.3 Review Strategy

Only one clinical trial was submitted for review, Protocol MO2-488.

4.4 Data Quality and Integrity

Because of the negative findings , DSI was not asked to perform a study audit.

4.5 Compliance with Good Clinical Practices

Study was carried out in accordance with ICH E6 Guidelines on Good Clinical Practice.

4.6 Financial Disclosures

Based on the Sponsor's submission of Forms FDA 3454 and 3455 (Financial Interests and Arrangements of Clinical Investigators) all disclosed financial interests were felt to not cause bias in the clinical study outcome.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetic

The absolute bioavailability of DEPAKOTE ER tablets administered as a single dose after a meal was approximately 90% relative to intravenous infusion.

As part of the written request the Sponsor was asked to perform a literature review of [pharmacokinetic parameter s in children. The Sponsor provided this, which was reviewed by clinical pharmacology. This will not effect labeling as no efficacy in the adolescent population was observed. The table below presents the final data from this review and includes a comparison to adult parameters. For more information the reader is referred to Dr. Tandon's review.

		Enzyme Uninduced		Enzyme Induced	
Pharmacokinetic Parameter	**Units**	**Child**	**Adult**	**Child**	**Adult**
C_{max}/Dose	(μg/mL)/(mg/kg/day)	4.4	5.6	2.2	4.1
T_{max}	h	1 to 4	3.0	1 to 4	3.1
$t_{½}$	h	9 to 15	14 to 16	5 to 9	9 to 12
C_{min}/Dose	(μg/mL)/(mg/kg/day)	2.3	4.2	1.0	2.1
V_d/F	mL/kg	0.23	0.12 to 0.19	0.23	0.12 to 0.19
Unbound Fraction	%	5.8 to 22	7 to 30	5.8 to 22	7 to 30
Clearance	mL/h/kg	15.0	9.0	27.5	15.8
Unbound Clearance	mL/h/kg	132	90	225	158

5.2Pharmacodynamics

No new information and not applicable.

5.3 Exposure-Response Relationships

Does not apply as there was an absence of evidence of effectiveness.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The FDA made a formal written request to Abbott Laboratories on January 31, 2006, pursuant to Section 505 A of the Federal Food, Drug and Cosmetic Act, that information be submitted from studies in migraine prophylaxis in the pediatric (adolescent) population. The objective of this study was to compare the safety and efficacy of Depakote ER to placebo in the prophylactic treatment of migraine headache in adolescents.

6.1.1 Methods

Efficacy was based on a single Phase 3, randomized, double-blind, placebo controlled, parallel-group, multicenter study which included 300 adolescent subjects with a history of migraine.

6.1.2 General Discussion of Endpoints

The Primary Efficacy Endpoint was the reduction from baseline in 4-week migraine headache rates as recorded by subjects in the Headache and Medication diary.

The Secondary Efficacy Endpoints used were:

- Percent reduction from baseline in 4-week headache rate; both actual rate and the proportion of subjects with at least 50% reduction
- Reduction from baseline in the number of migraine headache days per 4-week and for last 4-week period.
- Proportion of migraine headache free subjects, or those with at least a 75% reduction
- Change from baseline in the following variables:
    - PedMIDAS scores (The PedMIDAS is a validated and accepted endpoint which was developed to assess migraine disability in pediatric and adolescent patients, ages 4 to 18.)
    - Average functional ability/disability rating for migraine headaches
    - 4-week rates of migraine headaches with particular associated symptoms
    - Proportion of migraine headaches treated with particular symptomatic medications (E.G. triptans)
    - Average amount (e.g. number of doses) of the symptomatic medications used per migraine headache treated with that medication
    - Experimental Phase reduction from baseline in 4-week headache rate for all headaches

- Experimental Phase reduction from baseline in 4-week headache rate of headaches that subjects self-reported in the diary to be typical of migraine

6.1.3 Study Design

This was a Phase 3, randomized double-blind, placebo-controlled, parallel-group, multicenter study conducted in the United States. Approximately 300 adolescent subjects (i.e. 75 per treatment group) at 37 centers were randomized.

The maximum duration was 16 weeks, including a 2-week Washout Phase, a 4-week Baseline Phase and a 12-week Experimental Phase. Eligibility for enrollment in the Baseline Phase was based upon successful completion of the washout period and satisfaction of the appropriate inclusion and exclusion criteria. There were four equal arms in the Double-Blind Experimental Phase; 250 mg, 500 mg, 1000 mg and placebo.

6.1.4 Efficacy Findings

The primary endpoint, the Experimental Phase reduction from baseline in 4-week migraine headache rate, showed no dose response effect. The data was evaluated using a one-way ANOVA of rank-transformed data. These are presented in the table below.

Table 11. Experimental Phase Reduction From Baseline in 4-Week Migraine Headache Rate (Intent-to-Treat Dataset)

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a 50% reduction; and the Experimental Phase reduction from baseline in the number of migraine headache days per four weeks.

There were no statistically significant differences between any Depakote ER dose group and placebo for reductions from baseline in the number of doses of symptomatic medications used per migraine headache or in the proportion of migraine headaches treated with any symptomatic medication class.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Depakote ER did not differentiate from placebo in the prophylactic treatment of adolescent migraine headaches.

7 INTEGRATED REVIEW OF SAFETY

See separate safety review by Dr Sheridan.

7.1 Methods and Findings

7.1.1 Deaths

7.1.2 Other Serious Adverse Events

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

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7.1.3.3 Other significant adverse events

7.1.4 Other Search Strategies

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7.1.5.1 Eliciting adverse events data in the development program

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7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

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

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

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7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

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7.1.10 Immunogenicity

7.1.11 Human Carcinogenicity

7.1.12 Special Safety Studies

7.1.13 Withdrawal Phenomena and/or Abuse Potential

7.1.14 Human Reproduction and Pregnancy Data

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7.1.16 Overdose Experience

7.1.17 Postmarketing Experience

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7.2.1.2 Demographics

7.2.1.3 Extent of exposure (dose/duration)

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7.2.2.2 Postmarketing experience

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7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

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

7.2.8 Assessment of Quality and Completeness of Data

7.2.9 Additional Submissions, Including Safety Update

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

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7.4.2.2 Explorations for time dependency for adverse findings

7.4.2.3 Explorations for drug-demographic interactions

7.4.2.4 Explorations for drug-disease interactions

7.4.2.5 Explorations for drug-drug interactions

7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Does not apply as the efficacy trial has not led to approval.

8.2 Drug-Drug Interactions

No new information generated .

8.3 Special Populations

No efficacy was observed in adolescent patients.

8.4 Pediatrics

See above.

8.5 Advisory Committee Meeting

None

8.6 Literature Review

None

8.7 Postmarketing Risk Management Plan

No recommendations made.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

This reviewer agrees with the Sponsor, that Depakote ER did not differentiate from placebo in the prophylactic treatment of migraine headaches in adolescents.

9.2 Recommendation on Regulatory Action

It is recommended that these negative results be included in Depakote ER's labeling.

9.3 Recommendation on Postmarketing Actions

None.

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

9.5 Comments to Applicant

It is recommended that these results be included in Depakote ER's labeling.

10 APPENDICES

10.1 Review of Individual Study Reports

10.2 Line-by-Line Labeling Review

REFERENCES

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/s/

Norman Hershkowitz
5/19/2008 03:38:01 PM
MEDICAL OFFICER