`

CLINICAL REVIEW

Application Type	NDA
Submission Number	21168
Submission Code	SE5 015
Letter Date	September 24, 2007
Stamp Date	September 24, 2007
PDUFA Goal Date	March 24, 2008
Reviewer Name	Philip H. Sheridan, M.D.
Review Completion Date	March 21, 2008

Established Name Divalproex sodium

Trade Name (A) Depakote Sprinkle (NDA 19680)
(B) Depakote ER (NDA 21168)

Therapeutic Class	(A) Antiepileptic, (B) Migraine
Applicant	Abbott
Priority Designation	P
Formulation	(A) Sprinkle (B) Extended Release
Dosing Regimen	(A) BID, (B) Daily
Indication	(A) Partial Seizures, (B) Migraine
Intended Population	(A) Ages 3-10, (B) Ages 10-17 years

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

A pediatric Written Request was issued on August 9, 2002 (and revised on January 31, 2006) requiring information from pediatric bipolar, migraine prophylaxis, and epilepsy studies. The study reports for the completed required studies were submitted under this NDA submission by the Sponsor in response to this pediatric Written Request on September 24, 2007. The terms of the pediatric Written Request were met.

This review concerns the safety data from the efficacy and safety study (M02-488) and the two long-term safety studies for migraine prophylaxis (M02-554, M03-648) using Depakote ER and the long-term safety study for partial seizures (M04-714) using Depakote Sprinkle Capsules. These safety studies were submitted in response to that portion of the pediatric Written Request requiring long-term safety studies of valproate products in the treatment of children age 3-10 years for partial seizures and adolescents age 12-17 years for migraine prophylaxis.

The efficacy study for migraine prophylaxis (M02-488) and the efficacy and long-term safety studies for mania M01-342, M02-555, M03-647) have been reviewed in separate reviews of this NDA submission. No efficacy study for epilepsy was required under the revised pediatric Written Request since attempts by the Sponsor at recruitment for this study were not successful. Since both the bipolar and migraine prophylaxis efficacy studies failed to demonstrate efficacy, no new pediatric indications will result.

Additions to the Depakote ER label and the Depakote Sprinkle Capsules label will be made under heading 8 USE IN SPECIAL POPULATIONS – 8.4 Pediatric Use. These additions will describe the studies and their results including the resulting safety and adverse event information. Section 10.2 of this review gives the detailed recommendations for labeling.

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

A pediatric Written Request was issued on August 9, 2002 (and revised on January 31, 2006). In response to the pediatric Written Request, Depakote was studied in seven pediatric clinical trials. No efficacy study for epilepsy was required under the revised pediatric Written Request since attempts at recruitment by the sponsor for this study were not successful. The seven completed required studies were submitted under this NDA submission by the Sponsor on September 24, 2007. The terms of the pediatric Written Request were met.

Two of the seven pediatric studies were double-blinded placebo-controlled trials to evaluate the efficacy of Depakote for the indications of mania (150 patients aged 10 to 17 years, 76 of whom were on Depakote) and migraine (304 patients aged 12 to 17 years, 231 of whom were on Depakote). Efficacy was not established for either the treatment of migraine or the treatment of mania.

The remaining five trials were long-term safety studies. Two six-month pediatric studies were conducted to evaluate the long-term safety of Depakote ER for the indication of mania (292 patients aged 10 to 17 years). Two twelve-month pediatric studies were conducted to evaluate the long-term safety of Depakote for the indication of migraine (353 patients aged 12 to 17 years). One twelve-month study was conducted to evaluate the safety of Depakote Sprinkle Capsules in the indication of partial seizures (169 patients aged 3 to 10 years). The safety and tolerability of Depakote in pediatric patients were shown to be comparable to those in adults.

This review concerns the safety data from the efficacy and safety study and the two long-term safety studies for migraine prophylaxis and the long-term safety study for partial seizures.

1.3.2 Efficacy

Efficacy was not established for either the treatment of migraine or the treatment of mania.

1.3.3 Safety

The safety and tolerability of Depakote in pediatric patients were shown to be comparable to those in adults.

1.3.4 Dosing Regimen and Administration

No changes to current labeling from these safety studies.

1.3.5 Drug-Drug Interactions

No changes to current labeling from these safety studies.

1.3.6 Special Populations

Additions to the Depakote ER label and the Depakote Sprinkle Capsules label will be made under heading 8 USE IN SPECIAL POPULATIONS – 8.4 Pediatric Use. These additions will describe the studies submitted in response to the pediatric Written Request and their results including the resulting safety and adverse event information. Section 10.2 of this review gives the detailed recommendations for labeling.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

As in current and proposed labels for Depakote ER and Depakote Sprinkle Capsules.

2.2 Currently Available Treatment for Indications

Since both the bipolar and migraine prophylaxis efficacy studies failed to demonstrate efficacy, no new pediatric indications will result.

2.3 Availability of Proposed Active Ingredient in the United States

No change in current manufacture and marketing of Depakote ER and Depakote Sprinkle Capsules.

2.4 Important Issues With Pharmacologically Related Products

None

2.5 Presubmission Regulatory Activity

A pediatric Written Request was issued on August 9, 2002 (and revised on January 31, 2006) requiring information from pediatric bipolar, migraine prophylaxis, and epilepsy studies. The completed studies were submitted under this NDA submission by the Sponsor in response to this pediatric Written Request on September 24, 2007.

2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

As in current and proposed labels for Depakote ER and Depakote Sprinkle Capsules.

3.2 Animal Pharmacology/Toxicology

As in current and proposed labels for Depakote ER and Depakote Sprinkle Capsules.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

A. Antiepileptic

One twelve-month study (M04-714) was conducted to evaluate the safety of Depakote in the indication of partial seizures (169 patients aged 3 to 10 years).

B. Migraine

Two twelve-month pediatric studies (M02-554 and M03-648) were conducted to evaluate the long-term safety of Depakote for the indication of migraine (353 patients aged 12 to 17 years).

4.2 Tables of Clinical Studies

Phase 3 Safety Studies	Description
M04-714	One arm, open label, multicenter study to evaluate the long-term safety of valproate using Depakote Sprinkle Capsules in the treatment of partial seizures in children (n=169) age 3-10 years
M02-554	One arm, open label, multicenter study (extension of migraine prophylaxis efficacy study M02-488) to evaluate the long-term safety of valproate using Depakote ER for migraine prophylaxis in adolescents (n=112) age 12-17 years
M04-648	One arm, open label, multicenter study to evaluate the long-term safety of valproate using Depakote ER for migraine prophylaxis in adolescents (n=241) age 12-17 years

4.3 Review Strategy

The following documents were reviewed during the NDA review process

Submission date	Items Review
September 24, 2007	Study Reports M04-714, M02-554, M04-648 Integrated Summary of Safety Written Request terms (revised January 31, 2006) Sponsor-proposed labeling for Depakote Sprinkle Capsules and Depakote ER

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

Reviewed in separate review of migraine prophylaxis efficacy study M02-488.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

See current label.

5.2 Pharmacodynamics

See current label.

5.3 Exposure-Response Relationships

See current label.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Migraine prophylaxis: See separate review of study M02-488 under this NDA. Efficacy was not demonstrated.

Epilepsy: No efficacy study was required under the pediatric Written Request

Bipolar disorder: See separate review of study M01-342) under this NDA. Efficacy was not demonstrated.

The efficacy study for migraine prophylaxis and the efficacy and long-term safety studies for mania have been reviewed in separate reviews of this NDA submission. No efficacy study for epilepsy was required under the revised pediatric Written Request since attempts at recruitment for this study were not successful. Since both the bipolar and migraine prophylaxis efficacy studies failed to demonstrate efficacy, no new pediatric indications will result.

6.1.1 Methods

See 6.1 above.

6.1.2 General Discussion of Endpoints

See 6.1 above.

6.1.3 Study Design

See 6.1 above.

6.1.4 Efficacy Findings

See 6.1 above.

6.1.5 Clinical Microbiology

See 6.1 above.

6.1.6 Efficacy Conclusions

See 6.1 above.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This review concerns the safety data from the efficacy and safety study (M02-488) and the two long-term safety studies for migraine prophylaxis (M02-554, M03648) using Depakote ER and the long-term safety study for partial seizures (M04-714) using Depakote Sprinkle Capsules. These safety studies were submitted in response to that portion of the pediatric Written Request requiring long-term safety studies of valproate products in the treatment of children age 3-10 years for partial seizures and adolescents age 12-17 years for migraine prophylaxis.

A. Antiepileptic

Study M04-714 Description and Methods

M04-714 was a Phase 3 open-label, multi-center, outpatient study designed to evaluate the long-term safety of Depakote Sprinkle Capsules in the treatment of partial seizures, with or without secondary generalization, in children ages 3-10 years. This study consisted of a screening period followed by a 12-month treatment phase.

The study began with a 14-day screening phase in which all screening procedures were performed. The screening procedures included clinical laboratory assessments, vital signs (including height and weight), a neurological exam, and ECG. If the subject did not have an electroencephalogram (EEG) or Magnetic Resonance Imaging/Computed Tomography (MRI/CT) performed in the past, one was required at screening. Following screening, subjects entered the 12-month treatment period; the first study drug dose was dispensed on the day defined as Day 1. The study treatment period lasted approximately 12 months from the time of first study dose.

Subjects already taking valproic acid in a formulation other than Depakote Sprinkle Capsules at the time of study entry were converted to the Depakote Sprinkle Capsule formulation by the time they began treatment. There were no restrictions on the use of other AEDs during the study.

During the treatment phase, subjects were assigned to a dosing regimen of Depakote Sprinkle Capsules in a manner deemed clinically appropriate by the investigator. Total daily dose was to be determined by the investigator so as to achieve optimum clinical effect for each subject; with a target serum valproate concentration of 40 to 120 mcg/ml.

Subjects were required to return to the clinic for safety assessments at Months 1, 2, 3, 6, 9, and 12.

Safety was assessed by AE collection laboratory tests, vital signs, physical exams, brief neurological exams, and ECGs. The UKU Side Effect Rating Scale was used to assess movement-related side effects. The WASI or Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III), along with the Development Profile-II (DP-II), assessed neurocognitive status, and the BASC assessed behavioral status, respectively.

Blood samples for measurement of serum trough concentrations of total valproate were to be collected, via venipuncture, at the Months 1, 6, and 12 visits.

Study M04-714 Uniqueness

The duration of the long-term, open-label partial seizures study was 12 months. The partial seizures population was younger than the other two long-term safety study populations (ages 3-10 years, compared to 10-17 years for mania and 12-17 years for migraine prophylaxis), and also tended to have more comorbidities. In addition, subjects could be on concomitant anti-epileptic

drugs (AEDs) during the study, and over half of the subjects were taking valproic acid in the 30 days prior to the study, making direct comparisons of safety data between study populations difficult. The mean modal dose in the partial seizure epilepsy study, when adjusted for weight (22.1 mg/kg), was higher than for migraine prophylaxis (13.8 mg/kg).

B. Migraine prophylaxis

Studies M02-554 and M03 648 Description and Methods

There were two long-term safety studies of migraine prophylaxis. Study M02-554 was an extension study of the safety and efficacy study M02-488. M03-648 was a similar long-term safety study enrolling new patients.

M02-554

M02-554 was a Phase 3, open-label, multi-center 12-month extension study of Depakote ER in subjects who either completed or prematurely discontinued due to ineffectiveness from study M02-488, "The Safety and Efficacy of Divalproex Sodium Extended-Release Tablets in Migraine Prophylaxis: A Double-Blind, Placebo-Controlled Study in Adolescents."

Up to 300 subjects were expected to participate in the study. Study visits were conducted at Days 1 and 15 and Months 1, 2, 3, 6, 9, and 12. Subjects were instructed to take Depakote ER once daily at approximately the same time each day and to swallow the medication whole without cutting or chewing it.

Subjects were given Depakote ER 500 mg once daily for 15 days and then increased to 1000 mg once daily. The investigators could adjust the dose at any time, not to exceed 1000 mg per day and not to be less than 250 mg per day, to maintain a satisfactory clinical response. Data from the short-term study M02-488 are included in the M02-554 results only for subjects who were randomized to Depakote in the short-term study and who had a gap of seven days or less between the last dose of study drug in the short-term study and the first dose of study drug in the long-term extension study M02-554. For example, a subject who was treated with Depakote ER for 84 days in study M02-488, and was treated with Depakote ER for 100 days in study M02-554 (with no gap between the studies), would have 184 days of long-term Depakote ER exposure reported in the summary of long-term data, while a subject who was treated with placebo for 84 days in study M02-488 then was treated with Depakote ER for 100 days in study M02-554 would have 100 days of long-term Depakote exposure.

Safety was assessed by AE collection, laboratory tests, vital signs, and ECGs. Blood samples for measurement of serum trough concentrations of total valproate were to be collected, via venipuncture, at the Month 1, 2, 3, 6, 9, and 12 visits, approximately 24 hours (± 3 hours) after study drug dosing.

M03-648

M03-648 was a Phase 3, open-label, multi-center, long-term safety study of Depakote ER in subjects who had a diagnosis of migraine headaches consistent with IHS diagnostic criteria.

Up to 315 subjects were expected to participate in the study. The duration of the study was approximately 12 months, with study visits at Days 1 and 15 and Months 1, 2, 3, 6, 9, and 12.

Subjects were given Depakote ER 500 mg once daily for 15 days and then the dosage was increased to 1000 mg once daily. The investigators could adjust the dose at any time, not to exceed 1000 mg per day and not to be less than 250 mg per day, to maintain a satisfactory clinical response.

Safety was assessed by AE collection, laboratory tests, vital signs, physical exams, brief neurological exams, and ECGs. The UKU Side Effect Rating Scale was used to assess

Studies M02-554 and M03 648 Uniqueness

The duration of the two long-term, open-label migraine prophylaxis studies was 12 months. The migraine prophylaxis population is relatively healthy. Depakote doses for migraine prophylaxis are low compared to the doses used in the long-term safety studies for mania and partial seizures. The range of allowed doses for the migraine prophylaxis studies was 250 mg to1000 mg. In contrast, initial dosing for mania and partial seizures was weight-based and doses for each subject could be adjusted based on clinical effect or serum VPA concentrations.

7.1.1 Deaths

A. Antiepileptic

No deaths occurred in study M04-714

B. Migraine

No deaths occurred in studies M02-488, M02-554, or M03-648.

7.1.2 Other Serious Adverse Events

A. Antiepileptic

Eleven subjects (6.5%) experienced treatment-emergent SAEs during the partial seizures study.

Treatment-emergent SAEs experienced during the partial seizures study M04-714 are presented in Sponsor's Table 19 reproduced below from the Integrated Summary of Safety.

Table 19. Serious Adverse Events Experienced During the Partial Seizures Study M04-714

Investigator/ Subject Number	Gender/ Age	MedDRA Preferred Term/Reason Serious	Day Onset[a]	Days in Study	Severity	Relationship
[redacted]98805	F/3	Bronchitis chronic/ Hospitalization	363	372	Severe	Not related
[redacted]98807	M/8	Accidental overdose/ Hospitalization	-12	365	Severe	Not related
		Gastroenteritis/ Hospitalization	355		Moderate	Probably not related
[redacted]/98301	M/4	Pneumonia/ Hospitalization	151	161	Moderate	Not related
		Atelectasis/Prolonged Hospitalization	158		Moderate	Not related
		Empyema/Prolonged Hospitalization	165 (4)		Severe	Not related
[redacted]98308	F/7	Pyrexia[b]/ Hospitalization	322	325	Moderate	Probably related
[redacted]98603	F/9	Pneumonia/ Hospitalization	219	370	Severe	Not related
[redacted]98611	F/6	Pneumonitis/ Hospitalization	123	356	Mild	Not related
[redacted]91602	M/10	Encopresis/ Hospitalization	296	370	Severe	Not related
[redacted]91606	F/6	Shunt occlusion/ Hospitalization	183	263	Severe	Not related
		Hyperammonaemia[b]/ Hospitalization	260		Severe	Probably related
[redacted]91902	F/5	Pneumonia/ Hospitalization	316	361	Moderate	Probably not related
[redacted]92001	F/8	Lobar pneumonia[b]/ Hospitalization	92	154	Moderate	Not related
[redacted] 95003	M/9	Tibia fracture/ Hospitalization	296	358	Mild	Not related

a. Number in parentheses is days relative to last dose of study drug.
b. Classified as an AE resulting in premature discontinuation.

Subject 91606/[redacted] was admitted to the hospital on Study Day 260 due to mental status decline over the last several days. The subject appeared well the next day and was discharged from the hospital. A serum sample drawn in the hospital revealed an elevated ammonia level (225 mcmol/L) on Day 263 that resulted in the premature discontinuation of study drug. The investigator considered this SAE, which lasted 6 days, to be probably related to study drug.

Subject 98308/ was hospitalized on Study Day 322 due to a non-specific febrile syndrome (SAE of pyrexia) accompanied by nausea, vomiting, confusion, and diminished reactivity. Laboratory testing revealed elevated AST (3.5 × upper limit of normal [ULN]), ALT (1.8 × ULN), and amylase (1.4 × ULN) levels. None of the laboratory values for this subject were reported as AEs by the investigator. Study drug was decreased from 875 mg/day to 625 mg/day on Study Day 324, and then prematurely discontinued one day later. The investigator considered this SAE to be probably related to study drug.

All other SAEs were classified by the investigator and Sponsor as probably not or not related to study drug. This reviewer has reviewed the patient narratives included in the study report and agrees with this classification. The SAEs attributable to Depakote have been repeatedly documented in the medical literature and in previous clinical studies of adults and children over the age of 10. They are adequately discussed in the current and proposed labels for Depakote Sprinkles and Depakote ER.

B. Migraine

Fifteen subjects (4.2%) experienced treatment-emergent SAEs during the migraine prophylaxis studies. All of these SAEs were classified by the investigator and Sponsor as probably not or not related to study drug, with one exception. One SAE (hyperammonemia in study M02-554; Subject 22033/) was classified by the investigator as possibly related to study drug. This reviewer has reviewed the patient narratives included in the study report and agrees with this classification.

Treatment-emergent SAEs experienced during the migraine prophylaxis studies M02-554 and M03-648 are presented in the Sponsor's Table 18 reproduced below.

Table 18. Serious Adverse Events Experienced During the Migraine Prophylaxis Studies M02-554 and M03-648

Subject Number/Investigator	Gender/ Age	MedDRA Preferred Term/Reason Serious	Day of Onset[a]	Study Days Cumulative	Severity	Relationship
Study M02-554						
20214/[redacted]	M/17	Schizophreniform disorder/ Hospitalization	241 (21)	136/220	Severe	Not related
22030/[redacted]	M/12	Peptic ulcer/ Hospitalization	194	360/444	Severe	Probably not related
22033/[redacted]	F/14	Hyperammonaemia/ Required intervention	111	50/132	Severe	Possibly related
22228/[redacted]	F/14	Depressive symptom[b]	177 (1)	92/176	Severe	Not related
		Intentional self-injury[b]	177 (1)		Severe	Not related
		Skin laceration[b]	177 (1)		Severe	Not related
		Suicidal ideation[b]/ Hospitalization	177 (1)		Severe	Not related
22504/[redacted]	F/15	Abortion induced/Elective abortion Required intervention	457 (6)	372/451	Severe	Not related
Study M03-648						
81101/[redacted]	F/15	Depression[b]/ Hospitalization	255	260	Severe	Probably not related
81102/[redacted]	F/17	Abdominal pain lower/ Hospitalization	118	366	Severe	Not related
		Anorexia/ Hospitalization	118		Severe	Not related
		Nausea/Hospitalization	118		Severe	Not related
82501/[redacted]	M/14	Wrist fracture/ Required intervention	71	384	Mild	Not related
80123/[redacted]	F/15	Pneumonitis/ Hospitalization	35	367	Moderate	Not related
		Abortion induced/ Required intervention	299		Severe	Not related

a. Number in parentheses is days relative to last dose of study drug.

b. Classified as an AE resulting in premature discontinuation.

Table 18. Serious Adverse Events Experienced During the Migraine Prophylaxis Studies M02-554 and M03-648 (Continued)

Subject Number/Investigator	Gender/ Age	MedDRA Preferred Term/Reason Serious	Day of Onset[a]	Study Days Cumulative	Severity	Relationship
82106	F/17	Major depression[b]/ Hospitalization	110	110	Severe	Probably not related
80609/	F/16	Injury[b]/Hospitalization	200	267	Severe	Not related
		Suicidal ideation[b]/ Hospitalization	200		Severe	Not related
81902	M/12	Impulse-control[b] disorder/ Hospitalization	112 (1)	111	Severe	Probably not related
80504/	F/14	Abortion induced[b]/ Required intervention	32	32	Severe	Not related
82901	M/16	Migraine[b]/ Hospitalization	78 (20)	58	Severe	Not related
84303/	F/16	Post procedural vomiting/ Hospitalization	91	368	Severe	Not related
		Procedural pain/ Hospitalization	91		Severe	Not related

a. Number in parentheses is days relative to last dose of study drug.
b. Classified as an AE resulting in premature discontinuation.

Of note, Subject 22033/ experienced vomiting and grogginess in association with elevated ammonia level of > 250 mcmol/L and a valproate level of 179 mg/L (narrative presented in study M02-554, Section 14.3__3.2). The investigator considered this adverse event to be possibly related to study drug.

Subject 22228/ had SAEs of suicidal ideation, intentional self-injury, skin laceration, and depressive symptoms that resulted in hospitalization. Subject 80609 had SAEs of suicidal ideation and injury that also resulted in hospitalization. Two subjects had SAEs of depression (81101 and 82106). Depression was not recorded on the medical history for any of these subjects, although the narrative for Subject 82106 notes a "past history of being depressed."

This reviewer has reviewed the patient narratives included in the study report and agrees with this classification. The SAEs attributable to Depakote have been repeatedly documented in the medical literature and in previous clinical studies of adults and children over the age of 10. They are adequately discussed in the current and proposed labels for Depakote Sprinkles and Depakote ER.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A. Antiepileptic

Nine (9) out of 169 subjects (5.3%) prematurely discontinued study drug due to AEs in long-term safety study M04-714. Because only nine subjects had AEs that led to premature discontinuation in the partial seizures study M04-714, details for each subject are presented in Sponsor's Table 22 reproduced below in 7.1.3.2 (A).

B. Migraine

Fifty-five (55) out of 353 subjects (16%) prematurely discontinued study drug due to AEs in migraine prophylaxis long-term safety studies M02-554 and M03-648. The AEs that led to premature discontinuation in migraine prophylaxis studies M02-554 and M03-648 are summarized in decreasing order of frequency in Sponsor's Table 21 reproduced below in 7.1.3.2 (B).

7.1.3.2 Adverse events associated with dropouts

A. Antiepileptic

The following table 22 is reproduced from the Sponsor's Integrated Summary of Safety.

Table 22. Adverse Events Leading to Premature Discontinuation in Partial Seizures Study M04-714

Investigator/ Subject Number	Gender/ Age	MedDRA Preferred Term	Day of Onset[a]	Days in Study	Severity	Relationship
[redacted]98801	M/3	Abdominal pain	147	158	Moderate	PR
		Vomiting	147		Moderate	PR
		Diarrhoea	147		Moderate	PR
		Rash maculopapular	147		Moderate	PR
		Pain	147		Moderate	PR
		Decreased appetite	147		Moderate	PR
		Asthenia	147		Moderate	PR
		Nausea	147		Moderate	PR
		Faeces pale	147		Moderate	PR
		Hyperkinesia	159 (1)		Mild	PR
		Tremor	159 (1)		Mild	PR
[redacted]98803	F/6	Irritability	27	51	Moderate	PR
		Somnolence	27		Moderate	PR
		Fatigue	27		Moderate	PR
		Abdominal pain	27		Moderate	PR
[redacted]98301	M/4	Aspartate aminotransferase increased	159	161	Mild	PR
		Alanine aminotransferase increased	159		Mild	PR

PR = Probably Related

a. Number in parentheses is days relative to last dose of study drug. PR

b. Classified as an SAE.

Table 22. Adverse Events Leading to Premature Discontinuation in Partial Seizures Study M04-714 (Continued)

Investigator/ Subject Number	Gender/ Age	MedDRA Preferred Term	Day of Onset[a]	Days in Study	Severity	Relationship
[redacted]/98308	F/7	Pyrexia[b]	322	325	Moderate	PR
[redacted]/98117	M/4	Fatigue	236	249	Mild	Possibly related
[redacted]/90707	M/6	Psychomotor hyperactivity	8	40	Moderate	PR
[redacted]/91502	M/5	Feeling abnormal	3	31	Moderate	PR
		Somnolence	2		Moderate	PR
		Mood altered	2		Moderate	PR
[redacted]/91606	F/6	Hyperammonaemia[b]	260	263	Severe	PR
[redacted]/92001	F/8	Lobar pneumonia[b]	92	154	Moderate	Not related
		Weight increased	59		Moderate	PR

PR = Probably Related

a. Number in parentheses is days relative to last dose of study drug.

b. Classified as an SAE.

In summary, the most common AEs that resulted in premature discontinuation in more than one subject in the long-term partial seizures study were abdominal pain (n = 2), fatigue (n = 2), and somnolence (n = 2).

This reviewer has reviewed the patient narratives included in the study report of M04-714. I agree with the classification of relationship proposed by the investigator and Sponsor. The AEs attributable to Depakote have been repeatedly documented in the medical literature and in previous clinical studies of adults and children over the age of 10. They are adequately discussed in the current and proposed labels for Depakote Sprinkles and Depakote ER.

B. Migraine

The following table 22 is reproduced from the Sponsor's Integrated Summary of Safety.

Table 21. Adverse Events Leading to Premature Discontinuation in Migraine Prophylaxis Studies M02-554 and M03-648

MedDRA Preferred Term	Depakote ER (N = 353)
Any AE	55 (16%)
Weight increased	9 (3%)
Alopecia	6 (2%)
Nausea	6 (2%)
Ammonia increased	3 (< 1%)
Migraine	3 (< 1%)
Somnolence	3 (< 1%)
Abdominal pain	2 (< 1%)
Abdominal pain upper	2 (< 1%)
Depressed mood	2 (< 1%)
Depression	2 (< 1%)
Fatigue	2 (< 1%)
Irritability	2 (< 1%)
Menstruation irregular	2 (< 1%)
Suicidal ideation	2 (< 1%)
Abortion induced	1 (< 1%)
Acne	1 (< 1%)
Activated partial thromboplastin time abnormal	1 (< 1%)
Adnexa uteri pain	1 (< 1%)
Aggression	1 (< 1%)
Alanine aminotransferase increased	1 (< 1%)
Anhedonia	1 (< 1%)
Aspartate aminotransferase increased	1 (< 1%)
Asthenia	1 (< 1%)
Blood bilirubin increased	1 (< 1%)
Breast tenderness	1 (< 1%)
Chest pain	1 (< 1%)
Cognitive disorder	1 (< 1%)
Confusional state	1 (< 1%)
Constipation	1 (< 1%)
Crying	1 (< 1%)
Decreased appetite	1 (< 1%)

Table 21. Adverse Events Leading to Premature Discontinuation in Migraine Prophylaxis Studies M02-554 and M03-648 (Continued)

MedDRA Preferred Term	Depakote ER (N = 353)
Depressed level of consciousness	1 (< 1%)
Depressive symptom	1 (< 1%)
Disturbance in attention	1 (< 1%)
Dizziness	1 (< 1%)
Dysphagia	1 (< 1%)
Feeling jittery	1 (< 1%)
Gastritis	1 (< 1%)
Impulse-control disorder	1 (< 1%)
Infectious mononucleosis	1 (< 1%)
Injury	1 (< 1%)
Intentional self-injury	1 (< 1%)
International normalised ratio abnormal	1 (< 1%)
Leukopenia	1 (< 1%)
Lethargy	1 (< 1%)
Liver function test abnormal	1 (< 1%)
Major depression	1 (< 1%)
Mood swings	1 (< 1%)
Prothrombin level abnormal	1 (< 1%)
Prothrombin time abnormal	1 (< 1%)
Prothrombin time prolonged	1 (< 1%)
Rash papular	1 (< 1%)
Skin laceration	1 (< 1%)
Urinary tract infection	1 (< 1%)
Urticaria	1 (< 1%)
Vomiting	1 (< 1%)
White blood cell count decreased	1 (< 1%)

In summary, the AEs that resulted in premature discontinuation in more than three subjects in the long-term migraine prophylaxis studies were weight increased (9 subjects, 3%), alopecia (6 subjects, 2%), and nausea (6 subjects, 2%).

This reviewer has reviewed the patient narratives included in the study reports of M02-554 and M04-648. I agree with the classification of relationship proposed by the investigator and Sponsor. The AEs attributable to Depakote have been repeatedly documented in the medical literature and in previous clinical studies of adults and children over the age of 10. They are adequately discussed in the current and proposed labels for Depakote Sprinkles and Depakote ER.

7.1.3.3 Other significant adverse events

A. Antiepileptic

None.

B. Migraine

None.

7.1.4 Other Search Strategies

A. Antiepileptic

None.

B. Migraine

None.

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.

In migraine prophylaxis studies M02-554 and M03-648, symptoms associated with and occurring in conjunction with any migraine types previously experienced by a subject were not considered AEs. However, new migraine types or associated symptoms not previously

experienced by a subject occurring in conjunction with any migraine headache were considered AEs. Therefore, medical/surgical interventions or hospitalizations related to migraine headaches were not considered SAEs, unless related to another specific migraine type or the subject had new symptoms associated with his/her migraine headache.

In partial seizures study M04-714, seizures, including status epilepticus, were not captured as AEs. Changes in the type and frequency of seizures were captured in the seizure diary and reported as an assessment of efficacy. Likewise, hospitalization for seizures was not captured as an SAE. However, injuries sustained during, or secondary to, seizures were considered to be AEs and may have been SAEs if they met one or more of the SAE definitions.

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.

7.1.5.3 Incidence of common adverse events

A. Antiepileptic

Treatment-emergent AEs that occurred in $\geq$ 5% of the subjects in the partial seizures study M04-714 are summarized in decreasing order of frequency in Sponsor's Table 16 in 7.1.5.4 (A) below.

B. Migraine

Treatment-emergent AEs that occurred in $\geq$5% of the subjects in migraine prophylaxis studies M02-554 and M03-648 are summarized in decreasing order of frequency in Sponsor's Table 15 in 7.1.5.4 (B) below.

7.1.5.4 Common adverse event tables

A. Antiepileptic

Treatment-emergent AEs that occurred in $\geq$ 5% of the subjects in the partial seizures study M04-714 are summarized in decreasing order of frequency in Sponsor's Table 16.

Table 16. Summary of Treatment-Emergent Adverse Events That Occurred in at Least 5% of Subjects in Partial Seizures Study M04-714

MedDRA Preferred Term	Depakote Sprinkle Capsules Total (N = 169)
Any AE	138 (82%)
Pyrexia	30 (18%)
Cough	28 (17%)
Nasopharyngitis	23 (14%)
Vomiting	23 (14%)
Headache	20 (12%)
Nasal congestion	19 (11%)
Rhinorrhoea	18 (11%)
Upper respiratory tract infection	18 (11%)
Tremor	15 (9%)
Somnolence	13 (8%)
Diarrhoea	13 (8%)
Ear infection	12 (7%)
Pharyngitis	11 (7%)
Abdominal pain upper	10 (6%)
Bronchitis	10 (6%)
Fatigue	9 (5%)
Otitis media	9 (5%)
Pharyngolaryngeal pain	9 (5%)
Pneumonia	9 (5%)
Bronchospasm	8 (5%)
Decreased appetite	8 (5%)

Note: Subjects who reported the same preferred term two or more times are counted only once in the totals for that preferred term.

The majority of treatment-emergent AEs were mild to moderate in severity

The gastrointestinal AEs tended to appear early in the study and tended to be transient. Fatigue and tremor tended to appear in the first six months of the study, and tended to persist.

In summary, the eight most commonly experienced (> 10%) treatment-emergent AEs in the long-term partial seizures study were pyrexia (18%), cough (17%), nasopharyngitis (14%), vomiting (14%), headache (12%), nasal congestion (11%), rhinorrhoea (11%), and upper respiratory tract infection (11%).

B. Migraine

Treatment-emergent AEs that occurred in ≥5% of the subjects in migraine prophylaxis studies M02-554 and M03-648 are summarized in decreasing order of frequency in Sponsor's Table 15.

Table 15. Summary of Treatment-Emergent Adverse Events That Occurred in at Least 5% of Subjects in Migraine Prophylaxis Studies M02−554 and M03-648

MedDRA Preferred Term	Depakote ER (N = 353)
Any AE	302 (86%)
Nausea	61 (17%)
Vomiting	49 (14%)
Weight increased	46 (13%)
Upper respiratory infection	37 (10%)
Fatigue	28 (8%)
Nasopharyngitis	28 (8%)
Somnolence	28 (8%)
Migraine[a]	27 (8%)
Sinusitis	26 (7%)
Ammonia increased	19 (5%)
Gastroenteritis viral	17 (5%)
Pharyngolaryngeal pain	17 (5%)
Tremor	17 (5%)

a. An AE of migraine included new migraine types or associated symptoms not previously experienced by a subject.

Note: Subjects who reported the same preferred term two or more times are counted only once in the totals for that preferred term.

The majority of treatment-emergent AEs were mild to moderate in severity.

The gastrointestinal AEs tended to appear early in the study and tended to be transient. The increased weight, increased appetite, and fatigue also tended to appear early in the study, but tended to persist. Tremor appeared throughout the study and tended to persist.

In summary, the three most commonly experienced (> 10%) treatment-emergent AEs in the long-term migraine prophylaxis studies were nausea (17%), vomiting (14%), and weight increased (13%).

7.1.5.5 Identifying common and drug-related adverse events

A. Antiepileptic

See 7.1.5.4 (A) above

B. Migraine

See 7.1.5.4 (B) above

7.1.5.6 Additional analyses and explorations

A. Antiepileptic

None

B. Migraine

None.

7.1.6 Less Common Adverse Events

A. Antiepileptic

No significant additional adverse effects.

B. Migraine

No significant additional adverse effects.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Mean changes from baseline to minimum, maximum, and final value were summarized for laboratory parameters, along with shift tables for each indication. Laboratory values meeting potentially clinically significant criteria were identified and summarized by indication.

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

The two long-term safety studies for migraine prophylaxis (M02-554, M03-648) using Depakote ER and the long-term safety study for partial seizures (M04-714) using Depakote Sprinkle Capsules

7.1.7.3 Standard analyses and explorations of laboratory data

A. Antiepileptic

Hematology

A summary of mean changes from baseline to final values for hematology variables in partial seizures study M04-714 is presented in Sponsor's Table 26.

Table 26. Summary of Mean Changes from Baseline to Final Values for Hematology Variables in Partial Seizures Study M04-714

		Depakote Sprinkle Capsules	
Variable	**N[a]**	**Baseline**	**Mean Change (SD)**
Hemoglobin (g/L)	158	129.7	-1.6 (7.19)
Hematocrit (fraction)	158	0.388	-0.010 (0.025)
Red Blood Cells ($\times 10^{12}$/L)	158	4.52	-0.18 (0.305)
Platelet Count ($\times 10^{9}$/L)	157	304.3	-34.6 (59.10)
White Blood Cells ($\times 10^{9}$/L)	157	7.35	-0.32 (2.024)
Neutrophils (%)	162	46.5	-3.4 (13.13)
Lymphocytes (%)	162	42.7	2.5 (12.51)
Monocytes (%)	162	5.67	1.15 (3.018)
Eosinophils (%)	162	4.85	-0.33 (4.235)
Basophils (%)	162	0.30	0.04 (0.307)

a. Not all subjects had both baseline and on-treatment values.

In summary, the hematology variable that was associated with the largest change from baseline to final visit in the long-term partial seizure study was decrease in platelet count. No bleeding disorders were reported as AEs.

The effect of Depakote on coagulation and platelets is similar to that described in the current and proposed label.

Chemistry

Mean changes from baseline to final values for chemistry variables in partial seizures study M04-714 are presented in Sponsor's Table 29.

Table 29. Summary of Mean Changes from Baseline to Final Values for Chemistry Variables in Partial Seizures Study M04-714

Variable	N[a]	Depakote Sprinkle Capsules	
		Baseline	Mean Change (SD)
Glucose (mmol/L)	165	4.90	-0.09 (0.79)
Uric Acid (mcmol/L)	164	201.69	36.23 (50.02)
BUN (mmol/L)	165	4.75	0.44 (2.15)
Creatinine (mcmol/L)	165	51.83	-5.77 (8.06)
Total Protein (g/L)	165	69.42	1.45 (3.96)
Albumin (g/L)	165	42.62	1.39 (2.82)
Total Bilirubin (mcmol/L)	165	5.64	0.94 (2.28)
Alkaline Phosphatase (U/L)	165	226.99	-2.27 (63.40)
SGOT/AST (U/L)	165	24.61	4.19 (23.85)
SGPT/ALT (U/L)	165	13.75	0.51 (9.45)
Sodium (mmol/L)	165	139.51	0.69 (2.08)
Potassium (mmol/L)	165	4.30	0.00 (0.37)
Calcium (mmol/L)	165	2.38	0.00 (0.08)
Inorganic Phosphorus (mmol/L)	165	1.61	-0.03 (0.20)
Cholesterol (mmol/L)	165	4.07	0.00 (0.55)
Triglycerides (mmol/L)	165	1.00	0.10 (0.60)
Ammonia (mcmol/L)	150	52.22	-0.84 (30.04)
Amylase (U/L)	165	86.19	1.13 (21.62)

a. Not all subjects had both baseline and on-treatment values.

In summary, the chemistry variables that were associated with the largest changes from baseline to final visit in the long-term partial seizures study were increases in uric acid, total bilirubin, and AST, as well as decreased creatinine.

The effect of Depakote on serum chemistry is similar to that described in the current and proposed label.

B. Migraine

Hematology

A summary of mean changes from baseline to final values for hematology variables in the migraine prophylaxis studies M02-554 and M03-648 is presented in Sponsor's Table 25.

Table 25. Summary of Mean Changes from Baseline to Final Values for Hematology Variables in Migraine Prophylaxis Studies M02-554 and M03-648

		Depakote ER	
Variable	N[a]	Baseline	Mean Change (SD)
Hemoglobin (g/L)	334	137.1	-0.8 (7.64)
Hematocrit (fraction)	334	0.407	-0.002 (0.025)
Red Blood Cells ($\times 10^{12}$/L)	334	4.69	-0.08 (0.272)
Platelet Count ($\times 10^{9}$/L)	333	285.0	-24.4 (47.66)
White Blood Cells ($\times 10^{9}$/L)	334	6.58	-0.36 (1.676)
Neutrophils (%)	336	55.9	-1.4 (10.61)
Lymphocytes (%)	336	35.3	1.1 (9.96)
Monocytes (%)	336	5.42	0.45 (2.252)
Eosinophils (%)	336	3.01	-0.11 (2.167)
Basophils (%)	336	0.35	-0.03 (0.224)
Activated partial thromboplastin time (seconds)	253	31.1	0.2 (5.95)
Prothrombin time (seconds)	254	10.7	0.0 (2.01)
International normalized ratio	205	1.1	0.0 (0.13)

a. Not all subjects had both baseline and on-treatment values.

In summary, the hematology variable that was associated with the largest change from baseline to final visit in the long-term migraine prophylaxis studies was decrease in platelet count. No bleeding disorders were reported as AEs.

The effect of Depakote on coagulation and platelets is similar to that described in the current and proposed label.

Chemistry

Mean changes from baseline to final values for chemistry variables in the migraine prophylaxis studies M02-554 and M03-648 are presented in Sponsor's Table 28.

Table 28. Summary of Mean Changes from Baseline to Final Values for Chemistry Variables in Migraine Prophylaxis Studies M02-554 and M03-648

		Depakote ER		
Variable	N[a]	Baseline	Mean Change (SD)	
Glucose (mmol/L)	336	4.90	-0.02	(0.88)
Uric Acid (mcmol/L)	336	270.60	35.39	(58.17)
BUN (mmol/L)	336	4.34	0.06	(1.15)
Creatinine (mcmol/L)	336	73.65	-1.76	(10.93)
Total Protein (g/L)	336	72.63	-0.99	(4.02)
Albumin (g/L)	336	45.70	-0.75	(2.92)
Total Bilirubin (mcmol/L)	336	8.73	0.15	(4.16)
Alkaline Phosphatase (U/L)	336	177.49	-26.56	(47.72)
SGOT/AST (U/L)	336	19.84	-0.01	(10.90)
SGPT/ALT (U/L)	336	14.63	-0.43	(12.32)
Sodium (mmol/L)	336	141.60	-0.44	(2.57)
Potassium (mmol/L)	336	4.33	-0.02	(0.42)
Calcium (mmol/L)	336	2.41	-0.04	(0.10)
Inorganic Phosphorus (mmol/L)	336	1.43	-0.07	(0.23)
Cholesterol (mmol/L)	336	4.23	-0.19	(0.55)
Triglycerides (mmol/L)	336	1.36	0.00	(0.81)
Ammonia (mcmol/L)	332	40.52	12.92	(38.41)
Amylase (U/L)	335	77.06	-3.09	(15.84)
Total Testosterone (nmol/L)	50	1.53	0.23	(0.89)

a. Not all subjects had both baseline and on-treatment values.

In summary, the chemistry variables that were associated with the largest changes from baseline to final visit in the long-term migraine prophylaxis studies were increased uric acid, increased ammonia, and decreased alkaline phosphatase.

The effect of Depakote on serum chemistry is similar to that described in the current and proposed label.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Mean changes from baseline to minimum, maximum, and final value for vital sign values (i.e., heart rate, blood pressure, weight, height, and BMI) were summarized by indication. Values meeting potentially clinically significant criteria were identified and summarized by indication.

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

The two long-term safety studies for migraine prophylaxis (M02-554, M03-648) using Depakote ER and the long-term safety study for partial seizures (M04-714) using Depakote Sprinkle Capsules

7.1.8.3 Standard analyses and explorations of vital signs data

A. Antiepileptic

For partial seizures, mean increases from baseline to final values for body weight and height were 2.8 kg and 5.3 cm. BMI increased 0.3 kg/m2 from a baseline of 17.3 kg/m2.

Mean changes from baseline to final values for vital sign values for partial seizures study M04-714 are presented in Sponsor's Table 38.

Table 38. Summary of Mean Changes from Baseline to Final Values for Vital Sign Values in Partial Seizures Study M04-714

Vital Sign	N	Baseline Mean	Mean Change (SD) to Final	Minimum-Maximum Change to Final
Systolic blood pressure (mm Hg)	163	100.0	0.7 (12.22)	-35 – 38
Diastolic blood pressure (mm Hg)	164	62.3	1.3 (9.73)	-20 – 25
Heart rate (beats per minute)	159	88.8	-0.7 (13.59)	-38 – 44
Weight (lb)	164	57.0	6.3 (5.93)	-12.0 – 26.0
Weight (kg)	164	25.9	2.8 (2.70)	-5.0 – 12.0
Height (in)	163	47.5	2.1 (1.23)	0 – 7
Height (cm)	163	120.6	5.3 (2.93)	0 –18
BMI (kg/m^2)	163	17.3	0.3 (1.49)	-7 – 5

SD = standard deviation.

Fifteen subjects had potentially clinically significant vital sign values measured after baseline in the partial seizures study M04-714 (one subject had both low systolic blood pressure and low diastolic blood pressure, and one subject had both high diastolic pressure and elevated heart rate), including the following: high systolic blood pressure (2/163, 1%), high diastolic blood pressure (3/164, 2%), elevated heart rate (1/159, < 1%), low systolic blood pressure (1/163, < 1%), low diastolic blood pressure (5/164, 3%), and low heart rate (5/159, 3%).

The changes in vital signs do not require changes to current or proposed labeling.

B. Migraine

For migraine prophylaxis, mean increases from baseline to final values for body weight and height were 3.6 kg and 2.3 cm. BMI increased 0.7 kg/m2 from a baseline value of 23.3 kg/m2.

Mean changes from baseline to final values for vital signs in migraine prophylaxis studies M02-554 and M03-648 are presented in sponsor's Table 37.

Table 37. Summary of Mean Changes from Baseline to Final Values for Vital Sign Values in Migraine Prophylaxis Studies M02-554 and M03−648

Vital Sign	N	Baseline Mean	Mean Change (SD) to Final	Minimum-Maximum Change to Final
Systolic blood pressure (mm Hg)	347	110.1	0.7 (11.30)	-28 – 44
Diastolic blood pressure (mm Hg)	347	66.7	0.7 (8.68)	-26 – 34
Heart rate (beats per minute)	347	75.4	0.7 (12.76)	-47 – 40
Weight (lb)	347	139.3	8.0 (9.99)	-17 – 54
Weight (kg)	347	63.2	3.6 (4.57)	-7 – 25
Height (in)	347	64.6	0.9 (1.27)	-1 – 5
Height (cm)	347	164.0	2.3 (3.22)	-3 – 13
BMI (kg/m^2)	347	23.3	0.7 (1.42)	-4 – 6

SD = standard deviation.

Fifteen subjects had a potentially clinically significant vital sign value measured after baseline in the migraine prophylaxis studies M02-554 and M03-648: high systolic blood pressure (1/347, < 1%), low diastolic blood pressure (12/347, 3%), and elevated heart rate (2/347, < 1%)

In summary, mean changes from baseline to final values in systolic blood pressure, diastolic blood pressure, and heart rate were small in the long-term migraine prophylaxis studies. Mean increases from baseline in height, weight, and BMI were observed in these 12-month studies.

The changes in vital signs do not require changes to current or proposed labeling.

7.1.9 Electrocardiograms (ECGs)

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

Not applicable.

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

The two long-term safety studies for migraine prophylaxis (M02-554, M03-648) using Depakote ER and the long-term safety study for partial seizures (M04-714) using Depakote Sprinkle Capsules

7.1.9.3 Standard analyses and explorations of ECG data

Four subjects presented with ECG-related AEs in the long-term studies: two subjects in the mania studies M02-555 and M03-647 and two subjects in the long-term partial seizures study M04-714. There were no ECG-related AEs reported in the migraine prophylaxis long-term study. Details on these ECG-related AEs are presented in Sponsor's Table 39.

Table 39. ECG-Related Adverse Events

Investigator/ Subject Number	Gender/ Age	MedDRA Preferred Term	Day of Onset[a]	Severity	Etiology
Mania Study M02-555					
[redacted]/ 12401	F/10	Arrhythmia	189 (23)	Moderate	Unknown
Mania Study M03-647					
[redacted]70312	M/14	Electrocardiogram abnormal	54	Mild	EKG lead placement problem
Partial Seizures Study M04-714					
[redacted]/98801	M/3	Conduction disorder	159 (1)	Mild	Minimal conduction disorder
		Electrocardiogram abnormal	159 (1)	Mild	Minimal conduction disorder
[redacted]91604	M/8	Atrioventricular block first degree	373	Mild	Possible physiological variability from baseline
		Electrocardiogram abnormal	373	Mild	Possible physiological variability from baseline
		Sinus arrhythmia	373	Mild	Possible physiological variability from baseline

a. Number in parentheses is days relative to last dose of study drug.

No significant effects on the electrocardiogram requiring additions to the current or proposed labeling were identified.

7.1.10 Immunogenicity

Not addressed in these studies.

7.1.11 Human Carcinogenicity

Not addressed in these studies.

7.1.12 Special Safety Studies

Abnormal Movement Assessments

Six movement-related items from the neurological section of the UKU Side Effects Scale (dystonia, rigidity, hypokinesia/akinesia, hyperkinesias, tremor, and akathisia) were assessed in long-term studies for migraine prophylaxis (M03-648) and partial seizures (M04-714). These items were selected to evaluate the potential of study drug to cause extrapyramidal side effects. For each study separately, incidence of each side effect was summarized and a shift table was created for each side effect showing the number of subjects with each side effect absent or present at baseline and during the study. A side effect was categorized as absent during the study only if it was absent at each post-baseline assessment.

A. Antiepileptic (M04-714)

The number and percentage of subjects with each UKU side effect at each timepoint in partial seizures study M04-714 are presented in Sponsor's Table 42.

Table 42. UKU Side Effects at Each Scheduled Timepoint in Partial Seizures Study M04-714

UKU Side Effect	Baseline (N = 169)		Month 1 (N = 164)		Month 2 (N = 155)		Month 3 (N = 154)		Month 6 (N = 152)		Month 9 (N = 147)		Month 12 (N = 136)	
Any Neurologic Side Effect	28	(17%)	27	(16%)	31	(20%)	29	(19%)	26	(17%)	24	(16%)	25	(18%)
Dystonia	3	(2%)	3	(2%)	3	(2%)	4	(3%)	3	(2%)	3	(2%)	2	(1%)
Rigidity	5	(3%)	5	(3%)	5	(3%)	4	(3%)	3	(2%)	2	(1%)	2	(1%)
Hypokinesia/ Akinesia	2	(1%)	3	(2%)	2	(1%)	2	(1%)	2	(1%)	2	(1%)	1	(< 1%)
Hyperkinesia	9	(5%)	6	(4%)	7	(5%)	7	(5%)	7	(5%)	7	(5%)	5	(4%)
Tremor	14	(8%)	14	(9%)	17	(11%)	14	(9%)	14	(9%)	12	(8%)	16	(12%)
Akathisia	2	(1%)	2	(1%)	2	(1%)	2	(1%)	2	(1%)	2	(1%)	2	(1%)

OTE: Subjects who reported the same symptom two or more times are counted only once in the totals for that symptom.

At baseline, 17% of subjects had at least one movement-related side effect based on the UKU Rating Scale. The proportion of subjects with any neurologic side effects at each subsequent visit was similar to that at baseline.

With the exception of tremor, ≤2% developed each side effect after baseline. Of the 165 subjects with both a baseline and on-treatment UKU assessment, 13 (8%) had tremor during treatment but not at baseline, and one (< 1%) had tremor at baseline but not during treatment.

Tremor was reported as an AE in 15 (9%) subjects. The investigator rated the tremor as mild in severity for 13 subjects and moderate in severity for two subjects.

In summary, tremor was the most commonly observed UKU side effect observed in the long-term partial seizures study.

Tremor is a well documented, reversible adverse effect associated with valproate. These findings do not require any changes to the current or proposed labeling.

B. Migraine (M03-648)

The number and percentage of subjects with each UKU side effect at each timepoint in migraine prophylaxis study M03-648 are presented in Sponsor's Table 41.

Table 41. UKU Side Effects at Each Scheduled Timepoint in Migraine Prophylaxis Study M03-648

UKU Side Effect	Baseline (N = 237)		Month 1 (N = 219)		Month 2 (N = 208)		Month 3 (N = 195)		Month 6 (N = 154)		Month 9 (N = 134)		Month 12 (N = 114)	
Any Neurologic Side Effect	18	(8%)	13	(6%)	9	(4%)	10	(5%)	11	(7%)	9	(7%)	11	(10%)
Dystonia	1	(< 1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Rigidity	3	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(< 1%)	0	(0%)	0	(0%)
Hypokinesia/ Akinesia	0	(0%)	1	(< 1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Hyperkinesia	2	(< 1%)	0	(0%)	0	(0%)	0	(0%)	1	(< 1%)	0	(0%)	0	(0%)
Tremor	11	(5%)	12	(5%)	8	(4%)	10	(5%)	9	(6%)	9	(7%)	11	(10%)
Akathisia	6	(3%)	3	(1%)	3	(1%)	2	(1%)	2	(1%)	1	(< 1%)	1	(< 1%)

Note: Subjects who reported the same symptom two or more times are counted only once in the totals for that symptom.

At baseline, 8% of subjects had at least one neurological (movement-related) side effect based on the UKU Rating Scale. The proportion of subjects with any neurologic side effects at each subsequent visit was similar to that at baseline.

With the exception of tremor, < 1% of subjects developed each side effect after baseline. Of the 219 subjects with both a baseline and on-treatment UKU assessment, seven (3%) had tremor during treatment but not at baseline, and two (< 1%) had tremor at baseline but not during treatment.

For studies M02-554 (the long-term safety extension study) and M03-648 combined, tremor was reported as an AE in 17 (5%) subjects. The investigator rated the tremor as mild in severity for 14 subjects and moderate in severity for three subjects.

In summary, tremor was the most commonly observed UKU side effect observed in the long-term migraine prophylaxis studies.

Tremor is a well documented, reversible adverse effect associated with valproate. These findings do not require any changes to the current or proposed labeling.

Behavior Assessments

The Parent Rating Scale of the BASC was used to assess changes in problem and adaptive behaviors in long-term studies M03-648 (migraine prophylaxis) and M04-714 (partial seizures).

Scores on each subscale of the BASC were summarized using univariate statistics. The BASC has several age-appropriate versions. For migraine, the version for ages 12-18 years was used. For partial seizures, the versions for ages 2 1/2-5 years and 6-11 years were used. Because the

different versions do not have the same subscales, results are summarized separately for each version of the BASC within each indication.

A. Antiepileptic

Mean changes from baseline to the Month 6, Month 12, and final visits for BASC subscale scores for partial seizures study M04-714 are presented separately for the two age-appropriate versions of the BASC in Sponsor's Table 45.

Table 45. Summary of Mean Changes from Baseline to Final Values for BASC T-Scores by Age Group in Partial Seizures Study M04−714

Variable	6 Months		12 Months		Final	
	Baseline Mean	Mean Change (SD)	Baseline Mean	Mean Change (SD)	Baseline Mean	Mean Change (SD)
2.5 - 5 years	**N = 48**		**N = 33**		**N = 48**	
Problem Behaviors						
Hyperactivity	62.5	-0.5 (9.74)	62.3	2.6 (11.49)	62.5	1.0 (11.25)
Aggression	55.2	-1.8 (10.13)	55.1	-1.5 (10.66)	55.2	-2.2 (10.52)
Anxiety	55.9	-1.8 (9.58)	56.1	0.5 (11.82)	55.9	-0.4 (10.64)
Depression	56.5	-3.9 (11.28)	56.1	-3.0 (12.24)	56.5	-3.3 (11.67)
Somatization	61.1	-3.0 (11.54)	61.7	-3.8 (9.73)	61.1	-3.2 (10.42)
Atypicality	60.5	-4.5 (13.41)	61.1	-3.9 (15.22)	60.5	-3.4 (13.08)
Withdrawal	51.9	-3.2 (11.27)	51.0	-3.3 (8.89)	51.9	-3.1 (9.18)
Attention problems	64.6	-2.6 (16.47)	65.8	2.4 (17.76)	64.6	2.4 (17.08)
Adaptive Behaviors						
Adaptability	48.4	-1.3 (10.08)	48.7	-1.7 (8.29)	48.4	-1.5 (9.55)
Social skills	47.5	0.4 (7.94)	47.2	0.5 (6.12)	47.5	0.2 (6.39)
6-11 years	**N = 98**		**N = 86**		**N = 98**	
Problem Behaviors						
Hyperactivity	67.8	-1.8 (11.21)	66.9	-2.6 (10.63)	67.8	-2.5 (10.79)
Aggression	55.9	-1.9 (9.18)	55.5	-1.8 (11.31)	55.9	-2.1 (10.99)
Conduct problems	55.0	-1.6 (10.43)	54.4	-1.3 (11.42)	55.0	-1.1 (11.70)
Anxiety	48.7	-0.1 (8.69)	48.7	0.9 (7.86)	48.7	0.3 (8.18)
Depression	54.3	-1.2 (7.47)	53.9	-0.7 (9.79)	54.3	-1.0 (9.86)
Somatization	57.1	-0.3 (8.18)	56.7	-3.3 (9.81)	57.1	-2.8 (9.91)
Atypicality	61.5	-4.0 (11.54)	61.4	-5.8 (13.05)	61.5	-5.2 (12.94)
Withdrawal	51.5	-1.0 (9.25)	51.6	-2.3 (9.85)	51.5	-1.8 (9.50)
Attention problems	61.8	-0.4 (7.73)	61.5	-0.7 (8.86)	61.8	-0.5 (8.75)
Adaptive Behaviors						
Adaptability	44.3	0.9 (8.79)	45.1	0.7 (8.92)	44.3	0.7 (8.92)
Social skills	46.2	1.3 (8.43)	46.6	2.1 (8.84)	46.2	2.0 (8.73)
Leadership	42.7	-0.2 (7.31)	43.0	0.3 (9.17)	42.7	0.1 (9.14)

SD = standard deviation.
Note: T-scores for scales are age-specific. The Conduct problems subscale was not assessed for ages 2.5-5 years. For Problem Behaviors, lower scores represent better functioning. For Adaptive Behaviors, higher scores represent better functioning.

In summary, a small numerical improvement was observed in the partial seizures M04-714 study for mean scores in most subscales. The significance of this small improvement is uncertain given the open-label nature of the study, but it is reassuring that no significant worsening of scores was observed. No changes are required in current or proposed labeling.

B. Migraine

Mean changes from baseline to the Month 6, Month 12, and final visits for BASC subscale scores for migraine prophylaxis study M03-648 are presented in Sponsor's Table 44.

Table 44. Summary of Mean Changes from Baseline to Six-Month and 12−Month Values for BASC T-Scores for Children Ages 12-18 Years in Migraine Prophylaxis Study M03-648

	6 Months (N = 175)		12 Months (N = 124)		Final (N = 177)	
Variable	Baseline Mean	Mean Change (SD)	Baseline Mean	Mean Change (SD)	Baseline Mean	Mean Change (SD)
Problem Behaviors						
Hyperactivity	50.9	-0.8 (9.20)	51.1	-1.3 (11.77)	50.9	-1.0 (10.85)
Aggression	50.7	-1.0 (7.66)	50.6	-0.1 (10.39)	50.8	-0.1 (9.42)
Conduct problems	50.5	-0.2 (8.37)	49.9	0.9 (11.26)	50.5	0.9 (10.80)
Anxiety	52.2	-1.6 (8.03)	51.8	-2.7 (9.23)	52.3	-2.2 (8.77)
Depression	49.6	-1.5 (8.15)	49.2	-2.6 (8.46)	49.6	-1.9 (8.96)
Somatization	63.0	-5.4 (10.08)	61.8	-7.0 (10.71)	63.0	-6.2 (10.83)
Atypicality	49.3	-2.2 (8.11)	48.8	-1.7 (11.3)	49.4	-1.9 (10.60)
Withdrawal	50.2	-0.4 (9.63)	50.0	-2.0 (8.70)	50.3	-1.1 (9.15)
Attention problems	55.0	-0.5 (7.74)	55.3	-1.0 (8.84)	55.0	-0.2 (8.42)
Adaptive Behaviors						
Social Skills	49.5	-1.3 (7.20)	49.3	-1.6 (8.46)	49.4	-1.8 (8.47)
Leadership	50.0	-1.6 (7.17)	49.6	-1.0 (7.73)	50.0	-1.7 (7.74)

SD = standard deviation.
Note: For Problem Behaviors, lower scores represent better functioning. For Adaptive Behaviors, higher scores represent better functioning.

In summary, a small numerical improvement was observed in the migraine prophylaxis M03-648 study for mean scores in seven of eight problem behaviors. Small numeric worsening was seen for conduct problems, social skills, and leadership. The significance of this small overall improvement is uncertain given the open-label nature of the study, but it is reassuring that no significant worsening of scores was observed. No changes are required in current or proposed labeling.

Cognitive/Neuropsychiatric Assessments

Wechsler intelligence tests were used to assess changes in neurocognitive status in long-term studies M03-648 (migraine prophylaxis) and M04-714 (partial seizures). Scores on the WASI at each timepoint were summarized using univariate statistics for each study separately.

A. Antiepileptic

In study M04-714 (partial seizures), the DP II was used to assess function and development, and the WASI (ages $\geq$ 6) and WPPSI-III (one version for age 3 years, and one version for ages 4-5 years) were used to assess intelligence. Scores on the DP II, WASI, and WPPSI-III at each timepoint were summarized using univariate statistics.

The WPPSI-III was used for subjects between the ages of 3 and 5 and the WASI was used for subjects 6 years or older. For the children who were unable to take the age appropriate Wechsler scale, the DP-II was the only test used.

Mean changes from baseline to six-month, 12-month, and final values for IQ scores of the WPPSI-III and WASI for all children regardless of age in partial seizures study M04-714 are presented in Sponsor's Table 48.

Table 48. Summary of Mean Changes from Baseline to Month 6, Month 12, and Final Values for IQ Scores of WPPSI-III and WASI in Partial Seizures Study M04-714

	6 Months (N = 136)		12 Months (N = 115)		Final Value (N = 138)	
IQ Variable	Baseline Mean	Mean Change (SD)	Baseline Mean	Mean Change (SD)	Baseline Mean	Mean Change (SD)
Verbal Scale IQ	87.6	1.2 (8.92)	88.2	1.0 (9.24)	87.5	1.1 (8.88)
Performance Scale IQ	86.4	2.8 (7.16)	87.5	3.9 (9.93)	86.5	3.8 (9.61)
Full Scale IQ	85.0	1.9 (6.43)	85.8	2.3 (8.47)	85.0	2.2 (8.04)

SD = standard deviation.

In summary, in children between 3 and 10 years of age, all IQ scores from the WPPSI-III and WASI showed small numerical improvement from baseline to the six-month, 12-month, and end-of-treatment values in partial seizures study M04-714.

In the assessment of DP-II, developmental age was below chronological age, on average, for each domain for most age groups at all timepoints. In general, changes in the difference between developmental and chronological age were small over the 12-month study.

No changes in the current or proposed label are required by these findings.

B. Migraine

WASI in migraine prophylaxis study M03-648 are presented in Sponsor's Table 47.

Table 47. Summary of Mean Changes from Baseline to Six-month and 12−month Values for IQ Scores from the WASI in Migraine Prophylaxis Study M03-648

	Mean Change from Baseline to Six Months (N = 156)		Mean Changes from Baseline to 12 Months (N = 115)	
	Baseline Mean	Mean Change (SD) to 6 Months	Baseline Mean	Mean Change (SD) to 12 Months
Verbal Scale IQ	104.0	1.0 (8.06)	102.7	1.5 (8.54)
Performance Scale IQ	100.7	3.7 (7.73)	101.5	5.9 (6.83)
Full Scale IQ	102.7	2.7 (6.98)	102.4	4.3 (6.62)

SD = standard deviation.

In summary, all IQ scores from the WASI showed small numerical improvement from baseline to the end of treatment in migraine prophylaxis study M03-648.

The difference in cognitive neuropsychiatric assessment between the pediatric seizure population and the adolescent migraine population reflects the baseline differences in these populations with the seizure population having more comorbid neuropsychiatric problems.

No changes in the current or proposed label are required by these findings.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal Phenomena

Adverse events that started or worsened in severity more than one day after the last dose of study drug during the open period in the migraine prophylaxis and partial seizure studies were assessed..

Two AEs that were reported more than one day after the last dose of study drug in the open label period (all from the migraine prophylaxis studies) were identified as possible withdrawal/rebound-related AEs. Subject 22208[redacted], a 16-year old female, developed moderate nausea, stomach ache, diarrhea and vomiting beginning 5 days after the last dose of study drug, which the investigator interpreted as a drug withdrawal syndrome. The symptoms were not treated, and the AE lasted nine days. Subject 84501/[redacted]a 13-year old male, developed moderate pain in the suprapubic area that lasted for six hours and was considered by the investigator to be possibly related to study drug. The subject took study drug on Study Days 1 and 2, and the AE started on Study Day 4. Because the subject prematurely discontinued study drug for this adverse event, the Sponsor does not consider it to be withdrawal- or rebound-related.

There was no significant incidence of withdrawal phenomena requiring an addition to the current or proposed label.

Abuse Potential

There is no new information relevant to drug abuse from the studies.

7.1.14 Human Reproduction and Pregnancy Data

No new data.

7.1.15 Assessment of Effect on Growth

Growth was evaluated by assessing changes in the following measures: height, weight, and BMI. Growth-related measurements were performed at baseline, monthly for 3 months, at month 6, and at month 12 (when applicable).

There were no SAEs associated with height, weight, or BMI-related events.

Height

Baseline values and mean changes from baseline to final value for height are presented by indication in Sponsor's Table 56.

Table 56. Mean Change from Baseline to Final Values for Height by Indication

Indication	Height at Baseline (cm)	Mean Change from Baseline (SD) (cm)	Height at Baseline (in)	Mean Change from Baseline (SD) (in)
Mania (n = 257)	159.1	1.9 (2.81)	62.7	0.8 (1.11)
Migraine Prophylaxis (N = 347)	164.0	2.3 (3.22)	64.6	0.9 (1.27)
Partial Seizures (N = 163)	120.6	5.3 (2.93)	47.5	2.1 (1.23)

An increase from baseline in height was observed in studies for all indications. Increased height was reported as an AE in one (< 1%) subject in each of the long-term mania and migraine prophylaxis studies. In migraine prophylaxis study M03-648, Subject 80413/[redacted] had reported increases of 32 pounds and 3 inches after 93 days. In mania study M03-647, Subject 71517/[redacted] had reported increases of 25 pounds and 1 inch after 29 days. These AE did not result in premature discontinuation. There were no reports of height-related AEs in the long-term partial seizure study.

Weight

Eighteen subjects discontinued prematurely due to an adverse event of increased weight as follows. In the mania studies, one female subject had an AE of obesity while two male subjects

and five female subjects had AEs of increased weight. In the migraine studies, two male subjects and seven female subjects had AEs of increased weight. In the partial seizures study, one subject had an AE of increased weight. One subject in a mania study discontinued for an adverse event of decreased weight.

Increased weight was reported as an AE in 39 (13%), 46 (13%), and five (3%) subjects in the long-term mania, migraine prophylaxis, and partial seizures studies, respectively. Increased weight and increased appetite tended to appear early and to persist throughout the study.

Baseline values and mean change from baseline to final values for weight are presented by indication in Sponsor's Table 57.

Table 57. Mean Change from Baseline to Final Values for Weight by Indication

Indication	Weight at Baseline (kg)	Mean Change from Baseline (SD) (kg)	Weight at Baseline (lb)	Mean Change from Baseline (SD) (lb)
Mania (n = 257)	59.0	3.0 (3.87)	130.1	6.5 (8.46)
Migraine Prophylaxis (N = 347)	63.2	3.6 (4.57)	139.3	8.0 (9.99)
Partial Seizures (N = 164)	25.9	2.8 (2.7)	57.0	6.3 (5.93)

An increase from baseline in mean weight was observed in studies for all indications.

This is a previously described adverse effect of Depakote that requires no addition to the current or proposed label.

7.1.16 Overdose Experience

A number of subjects took prescribed Depakote doses that were higher than the maximum dose specified in the protocols for the long-term studies. In the mania studies, 7% (19/292) of subjects exceeded the protocol-specified maximum dose of 35 mg/kg, with one subject receiving a maximum dose of 61.2 mg/kg. In the migraine prophylaxis studies, one subject had a maximum dose of 1250 mg, which exceeded the protocol-specified maximum dose of 1000 mg. In the partial seizures study, one subject received a maximum dose of 62.5 mg/kg, which exceeded the protocol-specified maximum dose of 60 mg/kg. These prescribed doses that were beyond the dosing regimens that the protocols specified were defined as overdoses, but were not adverse events.

Four subjects, one in mania study M03-647 and three in partial epilepsy study M04-714, had AEs of Depakote overdose, as described below.

Depakote ER on Day 55 of the study. The investigator considered the AE to be moderate in severity, and no action was taken. No associated symptoms were reported.

In partial seizure study M04-714, three cases of Depakote overdose were reported. An 8-year-old male (98807) had an SAE of accidental overdose of 400 mg Depakote pills 12 days prior to study start. Associated symptoms included vomiting and abdominal pain, paresthesia in the hands, and unsteady gait. The subject was hospitalized.

An 8-year-old female (/98707) had an overdose of Depakote on Days 1 through 5 of the study. Her mother did not understand the titration instructions, and administered extra drug. The investigator considered the AE to be moderate in severity, and no action was taken. No associated symptoms were reported.

A 9-year-old male 98708) had an overdose of Depakote on Day 258 of the study. He took the morning dose twice. The overdose was followed by somnolence that lasted for six hours. The investigator considered the AEs to be mild in severity.

No modification of the label discussion of valproate overdose is required from these observations.

7.1.17 Postmarketing Experience

Not applicable

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

The number of subjects required to have six months (defined as at least 180 days) and 12 months (defined as at least 365 days) of exposure to Depakote in the Written Request is presented by indication in Sponsor's Table 3.

The terms of the Written Request were met.

Some subjects who completed the 6- and 12-month long-term studies took study drug for less than 180 and 365 days, respectively, and so are not included in Table 3.

Table 3. Number of Subjects Required to Have Six and 12 Months of Exposure to Depakote in the Written Request

	Mania		Migraine Prophylaxis		Partial Seizures	
Duration	**Required**	**Achieved**	**Required**	**Achieved**	**Required**	**Achieved**
6 months	100	119	150	237	N/A	N/A
12 months	N/A	N/A	75	150	50	100

For mania associated with bipolar disorder, the Written Request states: "A sufficient number of adolescent patients . . . must be enrolled to ensure that approximately 100 patients will be exposed to study drug for at least six months." In studies M02-555 and M03-647, 119 subjects had at least six months (i.e., 180 days) of exposure to Depakote ER. The overall mean (SD) duration of Depakote ER exposure was 122.7 (66.4) days. A total of 292 subjects were exposed to Depakote ER for 98.1 subject years in mania studies M02-555 and M03-647 (Sponsor's Table 4 in section 7.2.1.1 below).

7.2.1.1 Study type and design/patient enumeration

For migraine prophylaxis the Written Request states: "Enrollment must be adequate to obtain well-characterized safety data at clinically relevant doses from approximately 150 subjects in the relevant populations treated for six months and approximately 75 subjects treated for one year." In studies M02-554 and M03-648, 237 subjects had at least six months (i.e., 180 days) and 150 subjects had at least 12 months (i.e., 365 days) of exposure to Depakote ER. The overall mean (SD) duration of Depakote ER exposure was 266.1 (138.0) days. A total of 353 subjects were exposed to Depakote ER for 257.2 subject years in migraine prophylaxis studies M02-554 and M03-648 (Sponsor's Table 4).

For partial seizures, the Written Request states: "For the open-label, long-term safety study in partial seizures, approximately 50 patients, age 3 to 10 years, must be exposed to study drug for one year." In study M04-714, 100 subjects (59%) had at least 12 months (i.e., 365 days) of exposure to Depakote Sprinkle Capsules. The overall mean (SD) duration of Depakote Sprinkle Capsules exposure was 327.4 (97.4) days. A total of 169 subjects were exposed to Depakote Sprinkle Capsules for 151.5 subject years in the partial seizures study M04-714 (Sponsor's Table 4).

For the five safety studies combined, 814 subjects were treated for a total of 506.8 subject years.

Depakote exposure is presented by indication in Sponsor's Table 4.

Table 4. Number of Subjects and Subject-Years of Exposure to Depakote ER and Depakote Sprinkles Capsules

	Mania	Migraine Prophylaxis	Partial Seizures	Overall
Number of Subjects	292	353	169	814
Subject-years	98.1	257.2	151.5	506.8

7.2.1.2 Demographics

Demographic characteristics for each indication are shown in Sponsor's Table 8. Just over half of subjects in the migraine prophylaxis study population were female (54%), whereas the mania and partial seizures populations had more males than females (56% and 63%, respectively). The majority of subjects were white (79% of all study subjects). Subjects in the partial seizure study were younger (mean age = 6.5 years) and smaller (mean body mass index [BMI] = 17.3 kg/m2) than those in the mania studies (13.6 years, 22.9 kg/m2) and migraine prophylaxis studies (14.5 years, 23.3 kg/m2) (Table 8).

Table 8. Demographic Characteristics of Study Subjects by Indication

Demographic Characteristic	Mania Studies M02-555 and M03-647 N = 292		Migraine Prophylaxis Studies M02-554 and M03-648 N = 353		Partial Seizures Study M04-714 N = 169*	
Gender						
Female	128	(44%)	189	(54%)	63	(37%)
Male	164	(56%)	164	(46%)	106	(63%)
Race						
White	226	(77%)	267	(76%)	146	(86%)
Black	46	(16%)	73	(21%)	20	(12%)
American Indian/Alaska Native	2	(< 1%)	2	(< 1%)	0	
Asian	0		2	(< 1%)	0	
Mixed	8	(3%)	3	(1%)	0	
Other	10[a]	(3%)	6[b]	(2%)	3[c]	(2%)
Hispanic Ethnicity						
Yes	23	(8%)	18	(5%)	37	(22%)
No	269	(92%)	335	(95%)	132	(78%)
Age (years)						
Mean (SD)	13.6 (2.23)		14.5 (1.64)		6.5 (2.16)	
Range	9 - 17		11 - 18		3 - 10	
Height (cm)						
Mean (SD)	159.0 (12.31)		164.1 (9.50)		120.7 (13.72)	
Range	131.0 – 188.0		137.0 – 193.0		93.0 – 165.0	
Weight (kg)						
Mean (SD)	59.1 (20.50)		63.3 (17.14)		25.9 (9.53)	
Range	29.0 - 177.0		33.0 - 149.0		13.0 - 75.0	
BMI (kg/m^2)						
Mean (SD)	22.9 (6.04)		23.3 (5.23)		17.3 (3.24)	
Range	13.3 - 54.6		15.1 - 52.2		11.7 - 31.6	

BMI = body mass index; SD = standard deviation.
* N = 168 for weight and N = 167 for height and BMI.

7.2.1.3 Extent of exposure (dose/duration)

See 7.2.1.1

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable.

7.2.2.1 Other studies

7.2.2.2 Postmarketing experience

Not applicable.

7.2.2.3 Literature

Not applicable.

7.2.3 Adequacy of Overall Clinical Experience

The terms of the pediatric Written request were met.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable

7.2.5 Adequacy of Routine Clinical Testing

The terms of the pediatric Written Request were met.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable.

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

Not applicable.

7.2.8 Assessment of Quality and Completeness of Data

The terms of the pediatric Written Request were met.

7.2.9 Additional Submissions, Including Safety Update

Not applicable

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

Not applicable.

7.4 General Methodology

Not applicable.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable.

7.4.1.1 Pooled data vs. individual study data

Not applicable.

7.4.1.2 Combining data

Not applicable.

7.4.2 Explorations for Predictive Factors

Not applicable.

7.4.3 Causality Determination

Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Not applicable.

8.2 Drug-Drug Interactions

Not applicable.

8.3 Special Populations

See 1.3.6

8.4 Pediatrics

See 1.3.6

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

Not applicable.

8.7 Postmarketing Risk Management Plan

Not applicable.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

Two twelve-month pediatric studies were conducted to evaluate the long-term safety of Depakote in the indication of prophylactic treatment of migraine headaches (353 patients aged 12 to 17 years). One twelve-month study was conducted to evaluate the safety of Depakote in the

indication of partial seizures (169 patients aged 3 to 10 years). Overall, Depakote was generally well tolerated in pediatric subjects. No clinically meaningful differences between pediatric and adult subjects were observed in the long-term profile of Depakote treatment in the indications of migraine prophylaxis and partial seizures.

9.2 Recommendation on Regulatory Action

A pediatric Written Request was issued on August 9, 2002 (and revised on January 31, 2006) requiring information from pediatric bipolar, migraine prophylaxis, and epilepsy studies. The study reports for the completed required studies were submitted under this NDA submission by the Sponsor in response to this pediatric Written Request on September 24, 2007. The terms of the pediatric Written Request were met as discussed in Appendix 10.3 of this review.

This review concerns the safety data from the efficacy and safety study (M02-488) and the two long-term safety studies for migraine prophylaxis (M02-554, M03-648) using Depakote ER and the long-term safety study for partial seizures (M04-714) using Depakote Sprinkle Capsules. These safety studies were submitted in response to that portion of the pediatric Written Request requiring long-term safety studies of valproate products in the treatment of children age 3-10 years for partial seizures and adolescents age 12-17 years for migraine prophylaxis.

The efficacy study for migraine prophylaxis (M02-488) and the efficacy and long-term safety studies for mania M01-3428, M02-555, M03-647) have been reviewed in separate reviews of this NDA submission. No efficacy study for epilepsy was required under the revised pediatric Written Request since attempts by th e Sponsor at recruitment for this study were not successful. Since both the bipolar and migraine prophylaxis efficacy studies failed to demonstrate efficacy, no new pediatric indications will result.

Additions to the Depakote ER label and the Depakote Sprinkle Capsules label will be made under heading 8 USE IN SPECIAL POPULATIONS – 8.4 Pediatric Use. These additions will describe the studies and their results including the resulting safety and adverse event information. Section 10.2 of this review gives the detailed recommendations for 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

Additions to the Depakote ER label and the Depakote Sprinkle Capsules label will be made under heading 8 USE IN SPECIAL POPULATIONS – 8.4 Pediatric Use. These additions will describe the studies and their results including the resulting safety and adverse event information. Section 10.2 of this review gives the detailed recommendations for labeling.

9.5 Comments to Applicant

See 9.4.

10 APPENDICES

10.1 Review of Individual Study Reports

See section 7.

Line-by-Line Labeling Review

Pages 57 through 58 redacted for the following reasons:
- -
Pages removed for the following reason:

REFERENCES

None.

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

/s/

Philip Sheridan
3/24/2008 04:29:42 PM
MEDICAL OFFICER

Russell Katz
3/24/2008 04:35:16 PM
MEDICAL OFFICER