CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-168/S-007

MEDICAL REVIEW

Clinical Review and Evaluation of Supplemental NDA

NDA (Serial Number)	**21-168 SE5-007 Supplement**
Sponsor:	**Abbott Laboratories**
Drug:	**Divalproex Sodium Extended-Release (*Depakote ER*)**
Proposed Indication:	**Epilepsy in Children Age 10 Years and Older**

Material Submitted:

Draft Labeling Changes for Depakote ER

Final Clinical Study Report for M01-313: Evaluation of pharmacokinetic profile and safety of Depakote Extended Release tablets in pediatric patients

Correspondence Date:	**February 13, 2003**
Date Received Agency:	**February 14, 2003**
Date Review Completed	**August 5, 2003**
Reviewer:	**Philip H. Sheridan, M.D.**

1. Summary

This submission proposes new labeling changes for Depakote ER supported by the final report of Study M01-313 (Evaluation of pharmacokinetic profile and safety of Depakote-ER tablets in pediatric patients).

M01-313 was a Phase I multiple-dose, non-fasting, open-label, multiple center study designed to characterize the pharmacokinetics of Depakote ER in children (8-11 years; N=14) and adolescents (12-17 years; N=12). The pediatric pharmacokinetic profile was compared to a historical adult control group (Study M95-376).

The Sponsor proposes that these currently submitted results of Study M01-313 allow the recently approved adult epilepsy indication for Depakote ER to be extended to children down to age 10 years (thus making it essentially identical to the current epilepsy indication for Depakote DR, aka Depakote).

Study M01-313 is also an important component of the Sponsor's response to the Pediatric Written Request of August 9, 2002 since it contributes to the pharmacokinetic requirements of the Request.

Summary of Conclusions:

After reviewing this submission and the Clinical Pharmacology and Biopharmaceutics reviewer's report, this reviewer concludes that the results of M01-313 are valid and support the proposed use of Depakote –ER in children 10 years of age and older using the same dosing recommendations (on a mg/kg basis) used in adults.

However, the Sponsor-proposed labeling also refers [redacted] Therefore, several changes in the labeling language proposed by the Sponsor are required as indicated in Section 5 below.

2. Introduction and Regulatory History

Depakote ER was first approved for prophylaxis of migraine headaches in adults on August 4, 2000.

Depakote ER has only recently been approved for adult epilepsy (December 20, 2002). The Sponsor expects that these currently submitted results of Study M01-313 will allow the approved adult epilepsy indication for Depakote ER to be extended to children down to age 10 years (thus making it identical to the current epilepsy indication for Depakote DR, aka Depakote [NDA 18-273]).

Seven previous bioavailability studies (M95-272, M95-330, M98-937, M95-288, M95-376, M95-401, and M98-294) comparing equal doses of Depakote ER and Depakote DR in adults indicated that equivalent doses of Depakote ER resulted in 15-20% less AUC compared to Depakote DR.

Because of the lack of simple bioequivalence between equal doses of Depakote ER and Depakote DR, the Division issued a not-approvable letter on June 17, 1998 for NDA 20-782 (Depakote ER Tablets 500 mg). This NDA had sought approval for Depakote ER for the treatment of epilepsy. The Division was specifically concerned that, if epileptic patients used Depakote ER, the Cmin of Depakote ER might drop below the Cmin of the equivalent dose of Depakote DR and thus might allow breakthrough of seizures after conversion from DR to ER.

Subsequently, on August 4, 2000, the Division approved NDA 21-168 that provided a clinical efficacy study that demonstrating the safety and effectiveness of Depakote ER for **prophylaxis of migraine headaches in adults**.

In its **approval action letter of December 20, 2002**, the Division approved a restricted version (restricted to adults) of a labeling supplement (submitted on June 26, 2002, NDA 21-168 SLR-004) for Depakote ER. This labeling supplement included **guidelines for conversion from Depakote DR to Depakote ER in adult patients** and an **indication for adult epilepsy**. No efficacy studies for Depakote ER in adult epilepsy patients were required since the Sponsor had previously completed Depakote DR efficacy studies in epileptic patients (NDA 18-723).

The Division judged the conversion guidelines to be valid for adults on Depakote DR in the range of 500 mg daily to 3125 mg daily which would include most adults on either antiepileptic monotherapy or combination therapy. The conversion factor, originally derived from seven bioavailability studies (M95-272, M95-330, M98-937, M95-288, M95-376, M95-401, and M98-294) comparing equal doses of Depakote ER and Depakote DR, had been confirmed in study **M00-232** in adult volunteers and in **M01-274** in adult epileptic patients.

Study M00-232 in adult volunteers indicated the conversion scheme is appropriate for Depakote monotherapy up to 1250 mg/day.

Study M01-274 in adult epileptic patients (on a variety of concomitant antiepileptic drugs over a Depakote DR range up to 3,125 mg/day) indicated that the conversion scheme is appropriate for most adults on either antiepileptic monotherapy or combination therapy.

Fortunately, there was no evidence that the conversion factor differs between relatively low and relatively high dose Depakote DR within the dose range used by most adult patients.

Therefore, the approval action letter of December 20, 2002 gave Depakote ER the same epilepsy indication as Depakote DR in adults but not in children. Given that only sparse data was available for doses of Depakote above 3,125 mg daily, the proposed labeling for dose conversion was reworded to indicate that at higher Depakote-DR dosages there is insufficient data to allow conversion dose recommendation

For some drugs, a demonstration of bioequivalence in adults is accepted as indicative of bioequivalence in children as well. In expectation that such a consideration would be applicable to Depakote ER, **the Sponsor's originally proposed labeling language submitted on June 26, 2002 (NDA 21-168 SLR-004) included an indication for children down to age 10 years for Depakote-ER since Depakote-DR has this indication.**

However, the Division was uncertain that the same conversion factor (derived from two adult bioavailability studies) would apply to children. For example, the pediatric gastrointestinal tract might absorb Depakote ER either more or less efficiently than the adult gastrointestinal tract. The proposed labeling in this submission (Appendix 2, page 52) notes that "In some patients, many of whom have functional or anatomic (including ileostomy or colostomy) gastrointestinal disorders with shortened GI transit times, there have been postmarketing reports of Depakote ER tablets in the stool." The incidence might be higher in the pediatric population.

In fact, the Sponsor had previously acknowledged the uncertainty of the conversion factor for children. On January 3, 2001 during a face-to-face meeting with the Division about the limitations of Study M00-232, the Sponsor commented that children experience so much enzyme induction that conversion guidelines may be difficult and that it might be necessary to rely on therapeutic monitoring rather than a conversion factor when changing from DR to ER in children or in adults at higher DR doses. Although the subsequent Study M01-274 addressed the situation of higher DR doses in adults (up to 3,125 mg daily), it did not include any pediatric patients; the Division in discussing Study M01-274 with the Sponsor on May 3, 2001 again stated the need for future pediatric studies.

Furthermore, the currently submitted final report of Study M01-313 (Evaluation of pharmacokinetic profile and safety of Depakote extended release tablets in pediatric patients) was nearing completion at that time. During a teleconference with the Sponsor on December 17, 2002, the Division indicated that if the results of Study M01-313 clearly indicated that the adult guidelines for Depakote ER could be used for children as well, these results might be sufficient to allow the Depakote ER epilepsy indication and DR-to-ER conversion guidelines to extend down to children age 10 years or older.

In addition, the Agency expects to obtain pediatric labeling data for all valproate products from the future valproate pharmacokinetic studies that are being negotiated under the August 9, 2002 Pediatric Written Request (PWR). This PWR calls for pharmacokinetic, efficacy, and safety studies of valproate for three indications: partial seizures, migraine, and mania. The anticipated results of this study (M01-313) were specifically taken into account when the Division formulated the Pediatric Written Request letter (August 9, 2002). This Written Request includes the Pharmacokinetic Study in Pediatric Patients (3-17 years of age). The stated objective for this requested study (or studies) is "to characterize the pharmacokinetics of valproate in the pediatric patient population to determine age-appropriate dosing regimens in the pediatric efficacy and safety studies for the different indications described in this Written Request." In consideration of the anticipated results of M01-313, the Written Request further states "The pharmacokinetics of valproate must be evaluated after Depakote ER administration in patients aged 8 - 17 years or lower, if the lower age limit

specified in the inclusion criteria of the efficacy/safety study is <8 years." This statement acknowledges that M01-313 data (including children down to age 8) will potentially satisfy some of the pharmacokinetic study requirements of the Written Request (although the pediatric partial seizures efficacy and safety study proposed later in the text of the Written Request involves patients aged 3 years to 10 years and thus will require that the Sponsor first obtain further pharmacokinetic data down to age 3 years before choosing a dose regimen for the study).

Another study is

3. Financial Disclosure Statements for Study M01-313:

Study M01-313 had five study sites with five principal investigators and 24 sub-investigators/coordinators. Dr. Lawrence E. Roebel (Vice President, PPD Regulatory Affairs and Research Quality Assurance, Abbott Laboratories) has included with this submission a "Certification: Financial Interests and Arrangements of Clinical Investigators" (Form FDA 3454) which lists these investigators and certifies the absence of compensation from, of proprietary interest in, or of significant equity in Depakote ER or the Sponsor as defined in 21 CFR 54.2 (a & b). I conclude that there is no apparent potential influence on the study's conduct and results from these financial interests and arrangements.

4. Study M01 313

4.1 Objectives

Primary: To evaluate the pharmacokinetic profile and safety of Depakote-ER tablets at various doses given once daily in pediatric patients, aged 8-17 years.

Secondary: To compare the pharmacokinetic profiles pediatric patients, aged 8-17 years, to the profile of a healthy adult historical control group.

Design

A Phase I multiple-dose, non-fasting, open-label multiple center study to characterize the pharmacokinetics of Depakote ER in children (8-11 years; N = 14) and adolescents (12-17 years; N = 12).

All subjects in the study received Depakote ER.

Subjects currently taking Depakote DR had their total daily dosage converted to an equivalent (mg/mg) Depakote ER daily dose using 250 and 500 mg Depakote ER tablets, and they took this dose on Study Days 1 through 7 at approximately 0730 hours. Subjects currently taking Depakote ER maintained their current Depakote ER dose and took the dose at approximately 0730 hours from Study Days 1 through 7.

During nonconfinement on Study Day 1-6, study coordinators phoned the subject and/or parent at approximately 0730 and instructed the subject to take the dose at that time. On Study Days 7 and 8, subjects were confined to the study site. On Study Day 7, following breakfast (approximately 700 calories; approximately 40% fat) given at 0700, subjects were given the dose of Depakote ER at 0730.

Blood samples were collected pre-dose and at 3, 6, 9, 12, 15, 18, and 24 hours after the dose on Study Day 7. Subjects were also served lunch, followed by snack and dinner at standardized times on Day 7. Subjects were instructed not to consume grapefruit or grapefruit products within 3 days prior to the beginning of the study or during the study. Compliance with study medication was determined by pill count, and subjects who missed a dose should have been discontinued from the study.

4.2 Sample Size

Children (8-11 years; N = 14) and adolescents (12-17 years; N = 12).

4.3 Key Inclusion Criteria

Age 8 to 17 years

Assent/informed consent

Clinical diagnosis requiring administration of Depakote DR or Depakote ER.

Currently taking Depakote DR or Depakote ER and on a stable dose for a minimum of 7 days prior to screening

If on Depakote DR, total daily dose exactly divisible by 250.

If on Depakote ER, taken as QD morning regimen

Good general health (screening procedures include medical history, physical exam, vital signs, laboratory profile.)

4.4 Key Exclusion Criteria

Female patients of childbearing potential unless total abstinence or reliable birth control method

Female patients who were breastfeeding

Positive pregnancy test at screening or on day prior to drug administration

History of significant sensitivity to any drug

Use of OTC or prescription drugs, herbal supplements that could confound study results

Use of aspirin within 2 weeks of screening until end of study

Positive hepatitis screen

Recent donations or blood product transfusions

Use of nicotine products in 6 months prior to study

Recent investigational drug use

Episode of status epilepticus in 6 months prior to screening

Medical history of bowel disease or surgical procedure affecting g. i. motility

History of biochemical genetic, metabolic, hematological, pancreatic, or hepatic disorder

4.5 Concomitant Medications

The following are excluded:

Use of OTC or prescription drugs, herbal supplements that could confound study results

Use of aspirin within 2 weeks of screening until end of study

4.6 Dosage

Subjects were taking Depakote DR or Depakote ER and were on a stable dose for a minimum of 7 days prior to screening. Subjects currently taking Depakote DR had their Depakote DR total daily dosage converted to the same total daily dosage (mg/mg) of Depakote ER, and subjects currently taking Depakote ER continued with their current total daily dosage.

If the current total daily Depakote DR dose was not exactly divisible by 250, the subject was not eligible for enrollment into the study. This allowed for administration of the dosing using the 250- and 500- mg strength Depakote ER tablets.

4.7 Outcome Measure

Pharmacokinetic parameters of total and unbound valproate were determined using noncompartmental analysis.

Safety was evaluated based on vital signs, physical examinations, laboratory tests, and monitoring of adverse effects.

4.8 Outcome Measures and Analysis

Pharmacokinetic parameters of total and unbound valproate were determined using noncompartmental analysis. These included: C-max, AUC 0-24, C-min and degree of fluctuation (DFL). These parameters from the children and adolescents were compared to each other. Both were compared to an adult historical control (the 14 healthy adult volunteers in an open-label, non-fasting study [Regimen B of M95-376] who received 1000 mg of Depakote-ER QD).

4.9 Safety Monitoring

Safety was evaluated based on vital signs, physical examinations, laboratory tests, and monitoring of adverse effects. Laboratory test values identified as being potentially clinically significant according to predefined criteria were flagged and reviewed for clinical significance and relationship to Depakote ER.

4.10 Results

Demographics:

Twenty-nine subjects entered the study. Twenty-six completed and contributed to the pharmacokinetic analysis. The three withdrawals are discussed under **4.10 Results - Safety**.

Doses ranged from 250 mg to 1750 mg of Depakote ER once daily. The demographics are shown in the following Sponsor's table.

	Mean ± SD (Min – Max)		
	All Pediatric Subjects 8 to 17 years old (N = 29)	Children 8 to 11 years old (N = 14)	Adolescents 12 to 17 years old (N = 12)
Age (years)	12.1 ± 2.8 (8 – 17)	9.8 ± 1.2 (8 – 11)	14.8 ± 1.6 (13 – 17)
Weight (kg)	52.1 ± 24.9 (22.7 – 133.8)	35.5 ± 7.4 (22.7 – 48.1)	74.7 ± 22.6 (52.9 – 133.8)
Height (cm)	152.6 ± 15.9 (127.0 – 182.9)	140.8 ± 7.1 (127.0 – 158.0)	167.4 ± 8.8 (155.0 – 182.9)
BSA (m^2)	1.46 ± 0.39 (0.91 – 2.51)	1.18 ± 0.14 (0.91 – 1.46)	1.83 ± 0.27 (1.53 – 2.51)
Indication	9 Migraine (31.0%), 11 BPD (37.9%), 2 ADHD (6.9%), 7 Seizures (24.1%)	3 Migraine (21.4%), 3 BPD (21.4%), 1 ADHD (7.1%), 7 Seizures (50.0%)	5 Migraine (41.7%), 7 BPD (58.3%)

BSA = Body surface area
BPD = Bipolar disorder
ADHD = Attention deficit hyperactivity disorder

Only 7 patients (all in the 8-to-11-years-old group) had a seizure disorder as the reason for being treated with Depakote.

Pharmacokinetic:

The pharmacokinetic results are discussed in detail in the Clinical Pharmacology/Biopharmaceutics Review of this submission by Dr. Sally Usdin Yasuda. She concludes that: "The plasma concentration-time profiles were similar across the age groups as were the pharmacokinetic parameters. Children (ages 8-11), but not adolescents, appeared to have lower Cmax, AUC, and Cmin for total valproate than adults (approximately 20% lower) when these parameters were corrected for dose and weight. The moderate differences here reflect the inclusion of children in the lower end of the age range in the present study, and when only children 10 years of age and older were included, the weight corrected pharmacokinetic parameters were similar to those observed in adults. This is in agreement with information in the label of DEPAKENE (valproic acid capsules and syrup), noting that over the age of 10 years, children have pharmacokinetic parameters that approximate adults."

Summary/Conclusions:

Pharmacokinetic Results: The Depakote ER daily dose ranges and the measured C_{max}, C_{min}, and AUC_{24} pharmacokinetic parameter ranges are presented in the following table.

Group	N	Depakote ER Dose			VPA	Pharmacokinetic Parameters		
						C_{max}	C_{min}	AUC_{24}
		(mg)	(mg/m^2)	(mg/kg)		(µg/mL)	(µg/mL)	(µg•h/mL)
Children	14	250-1000	212–962	7.25–35.6	Total	55.7–132.7	8.9–108.6	954–2910
					Free	5.4–29.4	0.7–17.8	78.9–569
Adolescents	12	500-1750	199–951	3.74–20.6	Total	31.7–120.6	22.9–93.1	665–2700
					Free	3.2–28.1	1.8–16.9	56.4–545
Adults[§]	14[‡]	1000	474–628	11.0–18.4	Total	66.9–107.9	32.6–88.1	1200–2350
Adults[§]	15[¢]	1000	474–628	11.0–18.4	Total	66.9–137.4	32.6–88.1	1200–2540

§ Historical adult control group (Regimen B: 1000 mg extended-release divalproex sodium every 24 hours [q24h], non-fasting) from Study M95-376.

‡ Does not include Subject 15 who prematurely discontinued from the study and did not receive reference Regimen C, but completed Regimen B.

¢ All subjects who completed Regimen B

Mean (standard deviation) pharmacokinetic parameters of total and free VPA after administration of Depakote ER are listed in the following tables.

	Pharmacokinetic Parameters					
	Normalized by Dose/Body Surface Area			Normalized by Dose/Body Weight		
	C_{max} (ng/mL)/ (mg/m^2)	C_{min} (ng/mL)/ (mg/m^2)	AUC_{24} (ng•h/mL)/ (mg/m^2)	C_{max} (ng/mL)/ (mg/kg)	C_{min} (ng/mL)/ (mg/kg)	AUC_{24} (ng•h/mL)/ (mg/kg)
	Children: 8 to 11 years old (N = 14)					
Total VPA	177 (65.1)	109 (62.2)	3470 (1470)	5220* (1900)	3190* (1810)	102000* (42500)
Free VPA	26.6 (11.8)	12.9 (7.13)	458 (209)	772 (315)	370 (193)	13200 (5420)
	Adolescents: 12 to 17 years old (N = 12)					
Total VPA	141 (32.9)	93.5 (22.1)	2890 (558)	5670 (1500)	3790 (1170)	116000 (29400)
Free VPA	18.9 (8.25)	9.75 (3.59)	344 (134)	759 (335)	395 (168)	13900 (5770)
	Adults§: 18 to 55 years old (N = 14)‡					
Total VPA	160 (27.0)	104 (28.6)	3220 (617)	6180 (1160)	4020 (1140)	124000 (26100)
	Adults§: 18 to 55 years old (N = 15)¢					
Total VPA	164 (30.5)	107 (29.2)	3280 (637)	6270 (1170)	4080 (1120)	125000 (25500)

* Statistically significantly different from historical adult control group (ANOVA, $p < 0.05$).

§ Historical adult control group (Regimen B: 1000 mg extended-release divalproex sodium q24h, non-fasting) from Study M95-376.

‡ Does not include Subject 15 who prematurely discontinued from the study and did not receive reference Regimen C, but completed Regimen B.

¢ All subjects who completed Regimen B.

	Pharmacokinetic Parameters† (Cont.)				
	T_{max}	CL/F			DFL
	(h)	(L/h)	($L/h/m^2$)	(mL/h/kg)	
	Children: 8 to 11 years old (N = 14)				
Total VPA	9.9 (6.2)	0.401 (0.183)	0.336 (0.131)	11.2 (3.77)	0.545 (0.336)
Free VPA	8.8 (4.2)	3.53 (2.41)	2.89 (1.79)	94.3 (51.8)	0.790 (0.286)
	Adolescents: 12 to 17 years old (N = 12)				
Total VPA	10.8 (6.6)	0.653 (0.144)	0.358 (0.0641)	9.06 (2.03)	0.395 (0.107)
Free VPA	12.0 (5.3)	5.96 (2.07)	3.24 (0.951)	82.3 (28.2)	0.616 (0.204)
	Adults§: 18 to 55 years old (N = 14)‡				
Total VPA	15.9 (4.5)	0.600 (0.0986)	0.321 (0.0575)	8.37 (1.72)	0.432 (0.127)
	Adults§: 18 to 55 years old (N = 15)¢				
Total VPA	15.4 (4.7)	0.586 (0.109)	0.317 (0.0584)	8.29 (1.68)	0.435 (0.123)

† Parameters were not tested statistically.

§ Historical adult control group (Regimen B: 1000 mg extended-release divalproex sodium q24h, non-fasting) from Study M95-376.

‡ Does not include Subject 15 who prematurely discontinued from the study and did not receive reference Regimen C, but completed Regimen B.

¢ All subjects who completed Regimen B.

The comparisons of total VPA pharmacokinetics in children and adolescents *vs.* historical adults control group are presented in the following table.

Comparison	Pharmacokinetic Parameter	Central Values*		Ratio of Central Values	
		Test	Reference	Point Estimate+	95% Confidence Interval
	Without Dose Normalization				
Children *vs.* Adults§	C_{min} (μg/mL)	49.18	53.71	0.916	0.646 – 1.298
	C_{max} (μg/mL)	90.09	84.14	1.071	0.860 – 1.333
	AUC_{24} (μg•h/mL)	1735.60	1688.31	1.028	0.806 – 1.311
Adolescents *vs.* Adults§	C_{min} (μg/mL)	47.20	53.71	0.879	0.611 – 1.264
	C_{max} (μg/mL)	71.48	84.14	0.850	0.676 – 1.067
	AUC_{24} (μg•h/mL)	1471.25	1688.31	0.871	0.676 – 1.123
	Normalized by Dose per m^2 Body Surface Area				
Children *vs.* Adults§	C_{min}†	0.09	0.10	0.903	0.643 – 1.269
	C_{max}†	0.17	0.16	1.056	0.864 – 1.290
	AUC_{24}‡	3.21	3.17	1.014	0.815 – 1.261
Adolescents *vs.* Adults§	C_{min}†	0.09	0.10	0.904	0.634 – 1.288
	C_{max}†	0.14	0.16	0.874	0.709 – 1.076
	AUC_{24}‡	2.84	3.17	0.896	0.714 – 1.124
	Normalized by Dose per kg Body Weight				
Children *vs.* Adults§	C_{min}¢	2.70	3.88	0.697	0.496 – 0.978
	C_{max}¢	4.95	6.08	0.814	0.664 – 0.999
	$AUC_{24}$$	95.34	121.91	0.782	0.628 – 0.974
Adolescents *vs.* Adults§	C_{min}¢	3.63	3.88	0.936	0.657 – 1.332
	C_{max}¢	5.50	6.08	0.905	0.732 – 1.118
	$AUC_{24}$$	113.13	121.91	0.928	0.739 – 1.166

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

§ Historical adult control group (Regimen B: 1000 mg extended-release divalproex sodium q24h, non-fasting) from Study M95-376 (N=14).

† Dose per m^2 Body Surface Area normalized C_{min} and C_{max} units = (μg/mL)/(mg/m^2).

‡ Dose per m^2 Body Surface Area normalized AUC_{24} units = (μg•h/mL)/(mg/m^2).

¢ Dose per kg Body Weight normalized C_{min} and C_{max} units = (μg/mL)/(mg/kg).

$ Dose per kg Body Weight normalized AUC_{24} units = (μg•h/mL)/(mg/kg).

Safety:

All of the patients had been on Depakote DR or Depakote ER for variable periods of time (at least 7 days before screening) before entering this brief 8-day study. Therefore, it is not surprising that no significant adverse events attributable to the study drug occurred. Only 7 patients (all in the 8-to-11-years-old group) had a seizure disorder as the reason for being treated with Depakote. None reported exacerbation of their seizures during this brief study even though the protocol does not follow the recommended guidelines for converting from Depakote DR to Depakote ER.

There were no deaths.

Only one hospitalization occurred. Twenty-nine days after completing the study, **Subject 207**, a 13-year-old girl, was hospitalized for days because of nausea and vomiting. She was receiving Depakote ER 750-mg daily. On admission, amylase was 267 U/L (normal range 28-100 U/L) and lipase was 487 U/L (normal range 16-63 U/L). Depakote was discontinued, and the amylase and lipase returned to normal range before discharge from the hospital. The investigator concluded that the event was severe but not related to Depakote; he gave a diagnosis of "gastroenteritis". This patient may have had pancreatitis, but this entity is already a known adverse effect of valproate not requiring any labeling changes.

Three of the 29 subjects enrolled did not complete the study, but these withdrawals were not related to Depakote ER safety issues. One subject discontinued because he withdrew assent (Subject 107), one subject (Subject 209) was discontinued due to an adverse event (flu), and one subject (Subject 403) was discontinued when the Sponsor discovered a protocol violation (history of pyloric stenosis).

Subject 209 was a 13-year-old boy on 1500 mg of Depakote ER once daily. He reported a sore throat on Study Day 6 and "flu" (fever, body-ache, and headache) on Study Day 7. He was discontinued prior to the pharmacokinetic study. The investigator considered the event mild and not related to Depakote. ER.

Overall, treatment-emergent adverse events were reported in 41% of subjects (12/29) following administration of Depakote ER. Five subjects in the 8-11 year old group (5/15; 33.3%) and 7 subjects in the 12-17 year old group (7/14; 50%) reported at least 1 treatment-emergent adverse event. The most commonly reported adverse events were flu syndrome and headache. The majority of treatment-emergent adverse events were not considered to be related to study drug, and were considered to be mild or moderate in severity.

5. Reviewer's Comments on Proposed Labeling

The Clinical Pharmacology and Biopharmaceutics reviewer has suggested in her review that the Sponsor-proposed changes to the **CLINICAL PHARMACOLOGY** section for Special Populations (pediatric) be modified as follows (the change is highlighted):

"Valproate pharmacokinetic profile following administration of DEPAKOTE ER was characterized in a multiple-dose, non-fasting, open-label, multi-center study in children and adolescents. DEPAKOTE ER once-daily doses ranged from 250 to 1750 mg. Once-daily administration of DEPAKOTE ER in pediatric patients (10-17 years) produced plasma VPA concentration-time profiles similar to those that have been observed in adults."

This reviewer agrees with the Clinical Pharmacology and Biopharmaceutics reviewer since her proposed version makes clear to the reader that M01-313 supports use of Depakote ER in children age 10 and older.

In the opinion of this reviewer, the recommendation for use of Depakote ER in children younger than age 10 should depend on the additional pharmacokinetic and efficacy studies to be performed in response to the Pediatric Written Request of August 9, 2002. For this reason, several other changes in the Sponsor's proposed labeling are required.

INDICATIONS AND USAGE
Epilepsy
DEPAKOTE ER is indicated as monotherapy and adjunctive therapy in the treatment of adults and children 10 years of age and older with complex partial seizures . . . DEPAKOTE ER is also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures in adults and children 10 years of age and older, and adjunctively in adults and children 10 years of age and older with multiple seizure types that include absence seizures.

PRECAUTIONS
Pediatric Use
The safety and effectiveness of Depakote ER for the prophylaxis of migraine headaches . . .The safety and effectiveness of Depakote ER for the treatment of complex partial seizures, simple and complex absence seizures, and multiple seizure types that include absence seizures has not been established in pediatric patients under the age of 10 years.

DOSAGE AND ADMINISTRATION

Migraine
Depakote ER is indicated for prophylaxis of migraine headaches in adults. The recommended starting dose is . . .

Epilepsy
Depakote ER is indicated as monotherapy and adjunctive therapy for complex partial seizures and for simple and complex absence seizures in adult patients and pediatric patients 10 years of age or older.

Simple and Complex Absence Seizures for adults and children 10 years of age and older:

Conversion from DEPAKOTE to DEPAKOTE ER:
In adult patients and pediatric patients age 10 years of age and older with epilepsy previously receiving DEPAKOTE, DEPAKOTE ER should be administered . . .

6. Conclusions

After reviewing this submission and the Clinical Pharmacology and Biopharmaceutics reviewer's report, this reviewer concludes that the results of M01-313 are valid and support the proposed use of Depakote–ER in children 10 years of age and older using the same dosing recommendations (on a mg/kg basis) used in adults.

However, the Sponsor-proposed labeling also refers to the treatment of absence seizures without limiting this part of the seizure indication to patients age 10 and above.

Therefore, several changes in the labeling language proposed by the Sponsor are required as indicated in Section 5 just above.

Philip H. Sheridan, M. D.

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
8/14/03 01:51:13 PM
MEDICAL OFFICER

John Feeney
8/18/03 03:36:30 PM
MEDICAL OFFICER
concur