CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-168/S-007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	21-168 (SE5-007)
Brand Name:	Depakote ER
Generic Name:	Divalproex Sodium
Type of Dosage Form:	Extended Release Tablets
Strengths:	250 mg, 500 mg
Indications:	Epilepsy
Type of Submission:	Efficacy/Pediatric Supplement
Sponsor:	Abbott
Submission Dates:	February 13, 2003 June 3, 2003 July 24, 2003 July 25, 2003
OCPB Division:	DPE-I
OND Division:	Division of Neuropharmacological Drug Products HFD-120
OCPB Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCPB Team Leader:	Ramana Uppoor, PhD

1 Executive Summary

This NDA review evaluates a pharmacokinetic study following administration of DEPAKOTE ER in pediatric patients (8-17 years of age). The stated intention of the submission was to restore the pediatric indication for epilepsy consistent across Depakote products for DEPAKOTE ER (for 10-17 years of age). The study was also conducted as a partial response to a Pediatric Written Request (August 9, 2002) that was made to obtain pediatric information on valproate (VPA) in pediatric patients (3-17 years of age).

- The present study has met the objectives of characterizing the pharmacokinetics of valproic acid in pediatric patients, 8-17 years old and to compare the pharmacokinetic profiles following administration of Depakote ER in pediatric patients, 8-17 years old, to the profile of a healthy adult historical control group.
- 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.

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the submitted data in NDA 21-168/SE5-007 for DEPAKOTE ER in pediatric patients (8-17 years of age) acceptable.

1) Based on the above pharmacokinetic findings, the dosing recommendations for Depakote ER for children 10 years of age and older can be the same as the dosing recommendations (on a mg/kg basis) in adults in order to achieve comparable exposure.
2) The OCPB recommends minor changes in the labeling as described in section 3.2 of this review.

Please forward the labeling comments to the Sponsor.

Clinical Pharmacology and Biopharmaceutics Optional Intradivision Briefing:
August 5, 2003
Attendees: John Feeney, Sally Yasuda, Ramana Uppoor

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Reviewer, Neuropharmacological Drug Section, DPE I
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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

3.1 Background

DEPAKOTE (divalproex sodium; Delayed Release Tablets) is indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of 10 years, and in simple and complex absence seizures. DEPAKOTE is also indicated in adults for the treatment of acute manic episodes associated with bipolar disorder and for the prophylaxis of migraine headache. The current labeling for DEPAKOTE states that pediatric patients (i.e., between 3 months and 10 years) have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do adults, and that over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults. The current labeling for DEPAKOTE ER states that the safety and effectiveness for prophylaxis of migraine headaches and for treatment of epilepsy in pediatric patients has not been established.

The Sponsor was informed by the clinical division, at the time of approval of Depakote ER tablets for epilepsy, that the pharmacokinetic characterization in children following Depakote ER administration is necessary before labeling (indication) for 10-17 years can be allowed (due to concerns of potentially different gastric emptying characteristics that may affect pharmacokinetics with this extended release product).

A formal Written Request for pediatric studies on DEPAKOTE was made on August 9, 2002 in response to the Sponsor's Proposed Pediatric Study Request. Information was requested from studies in migraine prophylaxis, epilepsy, and bipolar disorder, including a pharmacokinetic study in pediatric patients (3-17 years of age).

3.2 Current Submission

The stated intention of the submission was to restore the pediatric indication for epilepsy consistent across Depakote products for DEPAKOTE ER (10-17 years of age). The present submission is also a partial response to the Pediatric Written request and consists of a Phase I, multiple-dose open-label, multiple-center study designed to evaluate the PK performance of DEPAKOTE ER in the pediatric population aged 8-17 years. The following clinical pharmacology study was submitted and reviewed:

- ABT-711/Protocol M01-313 – Evaluation of the Pharmacokinetic Profile and Safety Profile of Depakote Extended-Release Tablets in Pediatric Patients

The full review is found in the Appendix. The key findings with respect to the clinical pharmacology and Biopharmaceutics of DEPAKOTE ER in this pediatric population are as follows:

- The present study has met the objectives of characterizing the pharmacokinetics of valproic acid in pediatric patients, 8-17 years old and to compare the

pharmacokinetic profiles following administration of Depakote ER in pediatric patients, 8-17 years old, to the profile of a healthy adult historical control group.

- 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.

Based on the above pharmacokinetic findings, the dosing recommendations for Depakote ER for children 10 years of age and older can be the same as the dosing recommendations (on a mg/kg basis) in adults in order to achieve comparable exposure.

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the proposed label with respect to the pharmacokinetics information obtained in the present study to which the **CLINICAL PHARMACOLOGY** Section refers (note that we have not reviewed information regarding the effectiveness of DEPAKOTE ER for various indications). We have a minor change in the **CLINICAL PHARMACOLOGY** section for Special Populations (pediatric) 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."

Note: We have suggested deleting the [redacted] and adolescents in the study from the labeling. This makes the paragraph less confusing, and makes the labeling consistent with the dosing information (that is for children 10 years of age and older), and consistent with the labeled indications for other forms of Depakote in children 10 years of age and older.

We are aware [redacted] that will address other requirements of the Pediatric Written Request.

The OCPB finds that the submitted data in NDA 21-168 (S-007) is acceptable.

4 Appendices

4.1 Bioanalytical Methodology

Analytical Method for Determination of Free Valproic Acid in NDA 21-168 (SE5-007)

A gas chromatography (GC) method with flame ionization detection (FID) was developed at [redacted] and used for the analysis of free valproic acid in human plasma. [redacted] An aliquot of the organic phase is then analyzed by GC/FID.

Standard operating procedures (SOPs) were in place for sample preparation, the analytical procedure, for acceptance of the bioanalytical run (system suitability and acceptance of calibration standards and quality control (QC) samples), and acceptance criteria for subject samples.

Selectivity, Accuracy, Precision, and Recovery

Selectivity was determined by analysis of blank samples from 6 lots of control sodium heparinized human plasma. The validation report states that no significant interfering peaks due to endogenous compounds or reagents were observed at the retention times of free valproic acid or internal standard in 5 out of the 6 lots of control human plasma. There is no comment regarding the 6th lot. The representative chromatograms appear to be free of interfering peaks.

Ranges of the calibration curves, LOQ, and nominal values for the QC samples are shown in Table 1, below.

Table 1. Summary of standard curves and QC samples for Determination of Free Valproic Acid

Range of Calibration Curve	LOQ	QC Samples
[redacted]		

Standards for calibration curves were run in duplicate. Five sets of calibration curves were performed. Linearity was established [redacted] concentration^2 weighted linear regression analysis). The accuracy (calculated by Reviewer) and precision for each

standard ranged from [redacted] respectively, and are therefore acceptable.

Accuracy and precision were analyzed for [redacted] replicates of each of [redacted] quality control (QC) concentrations prepared in [redacted] with [redacted] sets of analysis performed on different days. Intra-day accuracy (calculated by Reviewer) and precision ranged from [redacted] respectively. Inter-day accuracy and precision ranged from [redacted] respectively, as calculated by the Reviewer. These values are acceptable.

Precision was also evaluated for [redacted] replicates of each of [redacted] QC samples ([redacted] total valproic acid) prepared in [redacted] with [redacted] sets of analysis performed on different days. Intra-day precision ranged from [redacted] and inter-day precision ranged (calculated by Reviewer) from [redacted] These values are acceptable. Since the QCs prepared in [redacted] represent the total valproic acid concentration, a nominal value for free valproic acid could not be obtained, and therefore accuracy could not be determined.

Stability

Stability of free valproic acid was demonstrated as follows. Nominal free valproic acid concentrations were estimated based on the mean values determined by the free valproic acid concentrations measured in the above study evaluating QC samples prepared in [redacted] in [redacted] was demonstrated after [redacted] For the low and high QC samples, the concentrations were within [redacted] of the presumed nominal concentration. For the middle QC samples 4/6 samples were slightly outside of the [redacted] range of the presumed nominal concentration resulting in an accuracy of approximately [redacted] samples was demonstrated at [redacted] for [redacted] Long-term stability of free valproic acid in [redacted] has been demonstrated for [redacted] at [redacted]°C (reported in analytical report for Study ABT-711/Protocol M01-313). Stability of stock solutions of valproic acid was demonstrated for [redacted] mg/ml for at least [redacted] at [redacted] in [redacted]. For the [redacted] µg/ml [redacted] solutions, stability was demonstrated for [redacted] at [redacted].

In conclusion, the analytical method used for analysis of free valproic acid in [redacted] samples in the clinical study in NDA-21-168 (SE5-007) is considered adequately documented and validated.

4.2 PK Study in Children

EVALUATION OF THE PHARMACOKINETIC PROFILE AND SAFETY OF DEPAKOTE EXTENDED-RELEASE TABLETS IN PEDIATRIC PATIENTS

Study Investigators and Site:
Gregory L. Kearns, PharmD
Children's Mercy Hospital
Kansas City, MO

Protocol Number: ABT-711/Protocol M01-313

OBJECTIVES:

To evaluate the pharmacokinetic profile and safety of Depakote Extended-Release (ER) tablets at various doses given once daily in pediatric patients, 8-17 years old. A secondary objective was to compare the pharmacokinetic profiles in pediatric patients, 8-17 years old, to the profile of a healthy adult historical control group.

FORMULATIONS:

Table 1. Products used in ABT-711/Protocol M01-313

	Bulk Product Lot Number	Exp Date (Dates of Study)
Depakote ER 250 mg tablets	74-038-4S	3/01/03 (10/14/01-7/27/02)
Depakote ER 500 mg tablets	76-661-AA-21	5/01/03 (10/14/01-7/27/02)

STUDY DESIGN:

This study was a multi-center, open-label, multiple-dose, non-fasting study. Subjects were enrolled to include 2 age groups, 8-11 years, inclusive and 12-17 years, inclusive. All subjects received Depakote ER. 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.

Inclusion criteria included pediatric male and female subjects between 8 and 17 years of age, inclusive. Subjects had a clinical diagnosis requiring the administration of Depakote DR or Depakote ER (on a stable dose for a minimum of 7 days prior to screening) and were otherwise in general good health. If the subject was on Depakote ER, it was a QD morning regimen. Females of childbearing potential were to have practiced a method of birth control that could include oral or parenteral contraceptives for 3 months prior to the screening. Subjects currently taking Depakote DR were not to include those with epilepsy. Exclusion criteria included over the counter or prescription medications which could confound the interpretation of study results (including herbal supplements, enzyme inhibitors/inducers) within 2 weeks before screening and during the course of the study, use of aspirin within 2 weeks prior to screening through study completion, receipt of any depot drug by injection (with the exception of contraceptive) within 30 days prior to screening, an episode of status epilepticus within the 6-month period prior to screening, tobacco or nicotine-containing products within the 6-month period prior to screening.

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.

ASSAY:

Plasma concentrations of total valproic acid were determined using a validated gas chromatography method with flame ionization detection. The analysis was performed by [redacted] The Sponsor has not provided the complete details of the validation of the method. However, this assay (performed by [redacted] was previously considered to be acceptable in the original NDA (20-782; OCPB review of June 1997). According to summary information provided in the present analytical report, valproic acid is stable in plasma for [redacted] at -20° C. The samples from the present study were stored at -20° C and, according to summary information provided by the Sponsor, were analyzed within the period for which stability in plasma has been demonstrated. Dilution integrity was demonstrated.

According to information provided in this submission, the assay for free valproic acid was validated and performed at [redacted]; (GC/FID Method Validation for the Determination of Free Valproic Acid in Sodium Heparinized Human Plasma; [redacted] Job Number: [redacted] (Lot: 001)). In the present submission it was determined that free valproic acid is stable in human plasma for at least [redacted] at -20° C. The samples from the present study were stored at -20° C and, according to summary information provided by the Sponsor, were analyzed within the period for which stability in plasma has been demonstrated.

Table 3. Performance of Analytical Method for ABT-711/Protocol M01-313

Analyte	Method	Standards (µg/ml)	Linearity	LOQ (µg/ml)	QC (µg/ml)	QC Inter-assay CV (%)	QC Inter-assay Accuracy (%)*
Total Valproic Acid	GC/FID	[redacted]					
Free Valproic Acid (prepared in [redacted])	GC/FID					[redacted]	
Free Valproic Acid (prepared in [redacted])				[redacted]	[redacted]		

*calculated by reviewer

A calibration curve (duplicate samples) and duplicate QC samples were analyzed with each batch of study samples. The calibration curves bracketed the range of plasma concentrations observed in the present study [redacted] µg/ml for total valproic acid; [redacted] µg/ml for free valproic acid). Although the lowest QC sample for valproic acid is not within 3x of the LLOQ, as recommended in the Guidance for Industry, the low QC sample is below the lowest total valproic acid plasma concentration, and can be considered to support the reliability of the standard curve in this particular study. The calibration curves were acceptable, with at least [redacted] of the points on each calibration curve falling within [redacted] of the nominal value (or [redacted] for the LOQ) for total valproic acid. (Of note, in run [redacted] the calibration curve was truncated to [redacted]

ug/ml. However, based on the sample results provided by the Sponsor, it does not appear that analytical samples were included in this run). For the QC samples, at least 83% of the values for each run fell within [redacted] of the nominal value for total valproic acid.

For free valproic acid the calibration curve and QC samples were prepared by [redacted] control [redacted] with known amounts of drug. The concentrations spanned the range of free valproic acid concentrations observed in the present study [redacted] µg/ml). A calibration curve (duplicate samples) and duplicate QC samples were analyzed with each batch of study samples. The calibration curves were acceptable, with at least [redacted] of the points on each calibration curve falling within [redacted] of the nominal value (or [redacted], for the LOQ) for free valproic acid. For the QC samples, at least [redacted] of the values for each run fell within [redacted] of the nominal value for free valproic acid.

In addition, for the free valproic acid assays, QC samples were prepared by [redacted], control human plasma with known amounts of drug. These QC samples were used to monitor the precision of the centrifuge procedure to obtain the [redacted] In 5 of the 6 runs, at least [redacted] of the values fell within [redacted] of the presumed nominal value. In the remaining run that was not the case, although not all replicates of the same concentration were outside the value. The nominal value in this case was based on mean values obtained during the method validation. However, since the QCs prepared in plasma represent the total valproic acid concentration, an actual nominal value for free valproic acid cannot be obtained, and therefore accuracy cannot be determined. The inter-assay precision for these QC samples is shown in the table above.

The performance of the assay for valproic acid is considered acceptable.

RESULTS:

Demographics

Twenty-nine subjects were enrolled in the study. Twenty-six subjects completed the entire study and were eligible for pharmacokinetic analysis (n=14 for 8-11 y.o., n=12 for 12-17 y.o.). One subject discontinued because he withdrew assent, one subject was discontinued due to an adverse event (flu), and one subject was discontinued due to a protocol violation (history of pyloric stenosis). Doses ranged from 250 mg to 1750 mg of DEPAKOTE ER once daily. Demographics of the subjects completing the study are shown below.

Table 4. Demographics of Subjects Completing the Study

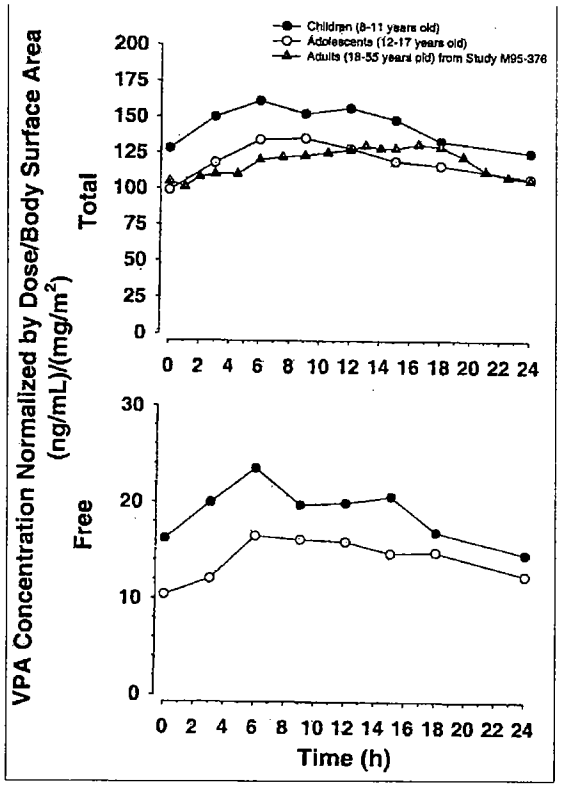
Mean Age (Range)	Weight (mean ± SD)	BSA (mean ± SD)	Gender	Race
9.8 (8-11)	35.5 ± 7.4 kg	1.18 ± 0.14 m^2	11 males 3 females	Black 1 White 11 Black/White 1
14.8 (13-17)	74.7 ± 22.6 kg	1.83 ± 0.27 m^2	5 males 7 females	Black 2 White 10

Pharmacokinetics

The Sponsor has used the scheduled times in the calculations of PK parameters. All samples collected 6 hours or less after dosing were obtained within 10% of the scheduled times; all samples collected more than 6 hours after dosing were obtained within 30 minutes of the scheduled times.

Pharmacokinetic parameters were determined using noncompartmental analysis. The Cmax for children (age range 8-11 y.o.) ranged from 55.7-132.7 ug/ml for total valproic acid following daily doses of 250-1000 mg of DEPAKOTE ER. The Cmax for adolescents (age range (12-17 y.o.) ranged from 31.7-120.6 ug/ml for total valproic acid following daily doses of 500-1750 mg of DEPAKOTE ER.

The plasma concentration time course for total as well as free valproic acid, normalized to either body surface area or weight, are shown in the figures below. The pertinent pharmacokinetic parameters for valproic acid are shown in Tables 5 and 6, below. The pharmacokinetic parameters for children and adolescents, calculated by the reviewer, are in agreement with those reported by the Sponsor. Plasma concentration collections in children were not sufficient to determine $t_{1/2}$. Pharmacokinetic parameters for free valproic acid for adults were not submitted.



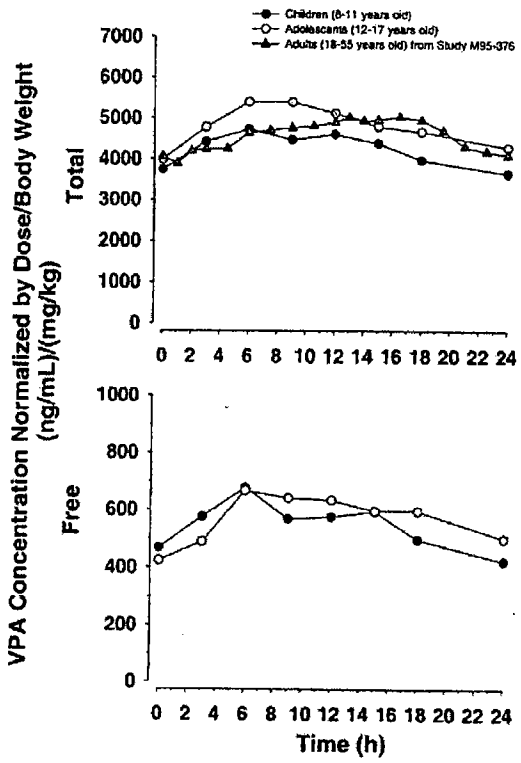


Table 5. Pharmacokinetic Parameters (Arithmetic Mean) for Valproic Acid

	Children (8-11 years) (% CV) n=14	**Adolescent (12-17 years)** (% CV) n=12	**Adults**[b] (%CV) n=14
Total Valproic Acid			
t_{max} (h)[a,b]	9.0 (3.00-24.00)	9.0 (3.00-24.00)	15.8 (7.50-24.00)
C_{max} (ng/mL)/(mg/kg)	5222 (36)	5667 (27)	6180 (19)
C_{max} (ng/mL)/(mg/m^2)	177 (37)	141 (23)	160 (17)
AUC_{0-24} (ng*h/mL)/(mg/kg)	102214 (42)	116193 (25)	124000 (21)
AUC_{0-24} (ng*h/mL)/(mg/m^2)	3475 (42)	2886 (19)	3220 (19)
Cl/F (ml/hr/kg)	11.1 (34)	9.1 (9)	8.4 (21)
Cl/F (L/h/m^2)	0.335 (0.3)	0.358 (0.3)	0.321 (18)
C_{min} (ng/ml)/(mg/kg)	3185 (57)	3786 (31)	4020 (28)
C_{min} (ng/ml)/(mg/m^2)	109 (57)	94 (24)	104 (27)
C_{last} (ng/ml)/(mg/kg)	3655 (51)	4294 (29)	
C_{last} (ng/ml)/(mg/m^2)	124.8 (51)	106.7 (24)	
Degree of Fluctuation (%)	54 (62)	39 (27)	43 (29)
Free Valproic Acid			
t_{max} (h)[a,b]	7.5 (3.00-18.00)	10.5 (6.00– 24.00)	
C_{max} (ng/mL)/(mg/kg)	772 (41)	759 (44)	
C_{max} (ng/mL)/(mg/m^2)	26.6 (44)	18.9 (44)	
AUC_{0-24} (ng*h/mL)/(mg/kg)	13241 (41)	13861 (42)	
AUC_{0-24} (ng*h/mL)/(mg/m^2)	458 (45)	344 (39)	
Cl/F (ml/hr/kg)	94.2 (55)	82.3 (34)	
Cl/F (L/h/m^2)	2.89 (62)	3.23 (29)	
C_{min} (ng/ml)/(mg/kg)	370 (52)	395 (43)	
C_{min} (ng/ml)/(mg/m^2)	12.9 (55)	9.7 (37)	
C_{last} (ng/ml)/(mg/kg)	423 (49)	501 (58)	
C_{last} (ng/ml)/(mg/m^2)	14.6 (51)	12.4 (51)	
Degree of Fluctuation (%)	79 (36)	62 (33)	

[a] median (range)
[b] as provided by Sponsor in Table 14.2_4.5 and Table 14.2_2.5

The plasma concentration-time profiles are relatively flat over the 24-hour dosing interval. The plasma concentration-time profiles are similar across the age groups. The Sponsor has used ANOVA to compare the pharmacokinetic parameters for total valproic acid in children, adolescents, and adults. According to those results, comparisons of Cmax, Cmin, and AUC without dose normalizations did not reveal statistically significant differences across the age groups, and the effect of age on total valproic acid Cmax, Cmin, and AUC24 (dose corrected and normalized for either weight or BSA) was not statistically significant. However, using pairwise comparisons for the dose per kg body weight normalized comparisons, total valproic acid Cmax, Cmin, and AUC for children were significantly lower than those for adults. According to calculations performed by the reviewer, these differences reflect an approximate 20% decrease in those values in children compared to adults. This is reflected in an approximate 32% increase in apparent oral clearance (dose per kg body weight normalized comparisons) in children compared to adults.

The Reviewer has calculated Cmax, Cmin, AUC, and clearance normalized for the dose per kg body weight in children 10 years of age and older. These results are shown in Table 6, below.

Table 6. Selected Pharmacokinetic Parameters (Arithmetic Mean) for Total Valproic Acid in Children (10-11 years old)

	Children (% CV) n=9
Total Valproic Acid	
C_{max} (ng/mL)/(mg/kg)	5827 (36)
AUC_{0-24} (ng*h/mL)/(mg/kg)	115970 (40)
Cl/F (ml/hr/kg)	10.0 (40)
C_{min} (ng/ml)/(mg/kg)	3832 (49)

In children 10 years of age or older, the Cmax, Cmin, and AUC (normalized for the dose per kg body weight) are not substantially different from those in adults (6%, 5%, and 6% lower, respectively), with an approximate 19% greater clearance in this age group than in adults.

The Sponsor used analyses of covariance (ANCOVA) to examine the effect of age, gender, body weight, or body surface area on valproic acid pharmacokinetic parameters, and found that body weight and body surface area were statistically significant (p=0.03) covariates of Cmax. The Sponsor also reports that age and gender were not statistically significant covariates of valproic acid pharmacokinetic parameters and that body weight and body surface area were not statistically significant covariates of AUC and Cmin.

The Sponsor also used the free and total valproic acid concentrations for nonlinear mixed effects analysis of protein binding. This was not part of the planned protocol analysis,

and will not be reviewed here. The Sponsor has also examined protein binding in terms of the relationship between free fraction and total valproic acid. The Sponsor reports that the free fraction (f_u) of valproic acid increased as a function of total concentration, such that at a total concentration of 50 mg/L, the f_u was approximately ——and at 150 mg/L the f_u was approximately —— This is in agreement with information currently in the label of DEPAKOTE ER that describes concentration dependent protein binding.

Safety

Treatment-emergent adverse events were reported in 41% of subjects (12/29) following administration of Depakote ER. Five subjects in the 8-11 y.o. group (5/15; 33.3%) and 7 subjects in the 12-17 y.o. 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.

CONCLUSIONS:

This study characterized steady state pharmacokinetic parameters of free and total valproic acid in children and adolescents following administration of DEPAKOTE ER. It also compared the pharmacokinetics of total valproic acid to historical data from adults.

The present study has met the objectives of characterizing the pharmacokinetics of valproic acid in pediatric patients, 8-17 years old and to compare the pharmacokinetic profiles in pediatric patients, 8-17 years old, to the profile of a healthy adult historical control group.

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.

It should be noted that according to the label of DEPAKENE (valproic acid capsules and syrup), pediatric patients (between 3 months and 10 years) have 50% higher clearance expressed on weight than do adults, and that over the age of 10 years, children have pharmacokinetic parameters that approximate adults.

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