

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-216**

**CLINICAL PHARMACOLOGY and**  
**BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

Gabapentin (Neurontin®)  
Oral solution (250 mg/5mL)

Pfizer (submitted by Parke-Davis  
Pharmaceutical Research)  
2800 Plymouth Road  
Ann Arbor, Michigan 48105

NDA 21-216  
NDA 20-235/S-015  
NDA 20-882/S-002

Submission Dates: December 14, 1999, August 16, September 1, 2000

Primary Reviewer: Maria Sunzel, Ph.D.

Pharmacometrics Reviewer: Elena Mishina, Ph.D.

Indication:

Submission Type: Original NDA at the time of submission (NDA 21-129, oral ) was approved after submission of NDA 21-216)

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**BACKGROUND**

Neurontin® (gabapentin) is currently approved for adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients with epilepsy (adults and children over 12 years of age). The approved pharmaceutical formulations for this indication are hard shell capsules (100, 300 and 400 mg), film-coated tablets (600 and 800 mg), and oral solution (250 mg/5 mL). The previous NDAs were approved in 1993 (NDA 20-235; capsules), 1998 (NDA 20-882; tablets) and on March 2, 2000 (NDA 21-129; oral solution). The dosing recommendations for the add-on therapy of gabapentin are 900-1800 mg/day divided into three daily doses.

This submission covers pharmacokinetic, safety and efficacy data to expand the use of gabapentin oral solution in patients under 12 years of age. The data in this application is also submitted as efficacy supplements to the previous NDAs for capsules (NDA 20-235/S-015) and tablets (NDA 20-882/S-002). The Sponsor received a final Written Request letter dated Oct 18, 1999, for pediatric studies of gabapentin.

In agreement with FDA, the present NDA, which includes safety and efficacy data for the use of gabapentin in patients under 12 years of age (1 month - 12 years of age), was submitted separately, as NDA 21-216. NDA 21-216 is cross-referenced to NDA 21-129, gabapentin which has been approved for adjunctive treatment of patients 12 years or older with epilepsy. The Clinical Pharmacology and Biopharmaceutics section of NDA 21-129 consisted of one bioequivalence study that showed bioequivalence between single doses of 300 mg administered as or capsules in healthy adult volunteers. This information is covered in the CPB review of NDA 21-129, dated September 20, 1999.

NDA 21-216 contains the following clinical pharmacology data:

- Two traditional pharmacokinetic studies evaluating the pharmacokinetic studies of gabapentin administered as or capsules to healthy subjects aged 1 month - 12 years.
- A population pharmacokinetic analysis with data from five phase II-III studies in patients aged 2 months - 13 years, with sparse blood sampling, and the two traditional pharmacokinetic studies.

The clinical section of the current NDA contains safety data in pediatric patients 1-month to 13 years of age, and efficacy data in pediatric patients 1-month to 12 years of age for both the and capsule dosage forms.

## EXECUTIVE SUMMARY

The sponsor is proposing Neurontin®. Efficacy has not been established in pediatric patients below the age of 3 years. The proposed gabapentin dosing recommendations for pediatric patients is 30 mg/kg/day, given in divided doses (three times a day).

From the submitted data regarding gabapentin pharmacokinetics in children between the ages 1 month – 13 years, it can be concluded that,

- Oral clearance of gabapentin is directly proportional to creatinine clearance
- Oral clearance is approximately 30% higher in children below the age of 5, also after adjustment for body weight (traditional and population pharmacokinetic analyses)
- Maximum plasma concentrations are reached approximately 2 hours after oral gabapentin administration as capsules or solution
- The terminal half-life of gabapentin is similar in children (4.7 h) and adults (5-7 h)
- The pharmacokinetics of gabapentin is similar in adults and children older than 4 years
- The influence of body surface area, gender, height, formulation, disease, co-administration of phenytoin, phenobarbital, valproic acid, carbamazepine and vigabatrin on clearance was not statistically significant, based on population data analysis
- The influence of age, gender, race and formulation on volume of distribution of gabapentin was not statistically significant, based on population data analysis

Minor revisions of the sponsor's proposed label are suggested by the Office of Clinical Pharmacology and Biopharmaceutics, as described in the section 'LABELING REVISIONS'.

available, this information will not be included in the label text according to the Medical Division (HFD-120).

**APPEARS THIS WAY  
ON ORIGINAL**

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### Pharmacokinetics of gabapentin

The pertinent pharmacokinetic properties of gabapentin described (PDR 2000) are;

- A bioavailability of about 60 percent in the dose range of 300 to 600 mg T.I.D., although the bioavailability decreases by 25% after a 400 mg dose compared to 100 mg gabapentin
- No effect of food on the rate and extent of absorption
- Low plasma protein binding (<3%) with an apparent volume of distribution of  $58 \pm 6$  L (mean  $\pm$  SD)
- Distribution over the blood-brain barrier (CSF concentrations are approximately 20% of the corresponding plasma concentrations at steady state)
- Renal excretion without metabolism as the major elimination pathway
- Renal clearance directly proportional to creatinine clearance
- A terminal half-life of 5 to 7 hours after single and repeated doses, which is prolonged in elderly and renally impaired patients (hepatic impairment not studied)
- Similar pharmacokinetics in males, females and children >12 years old

**Study #1. Report RR-744-00377: A single dose study of Neurontin® (gabapentin; CI-945) pharmacokinetics in healthy pediatric subjects (protocol 945-202)**

(NDA 21-216 volume 3)

#### Objective

The aim of the study was to characterize single-dose pharmacokinetics of gabapentin in healthy pediatric subjects.

#### Study Design and Demographics

This was an open-label, single dose study in 24 children (Caucasian, 7F/17M). The mean  $\pm$  SD (range) age, weight and height of the subjects were  $8.7 \pm 2.8$  (4-12) years,  $33.8 \pm 10.6$  (16-52) kg and  $133.6 \pm 14.8$  (105-159) cm. The subjects were divided into three groups according to weight, 16-25 kg, 26-36 kg and 37-50 kg. The respective group were given 200 mg (n=7), 300 mg (n=8) and 400 mg (n=9) gabapentin according to body weight. The doses were chosen to correspond to approximately 10 mg/kg for all subjects participating in the study. The capsule formulations were administered in the morning after an 8-h fasting period.

Frequent blood samples (n=11) were drawn and urine collected in intervals (n=4) up to 24 h after drug administration.

#### Bioanalytical Methods

Plasma and urine concentrations of gabapentin were determined by the use of a validated HPLC procedure with UV detection. The methods were validated over the concentration ranges of \_\_\_\_\_  $\mu$ g/mL in plasma, and \_\_\_\_\_ /mL in urine.

**Pharmacokinetic Analysis**

Pharmacokinetic parameters ( $C_{max}$ ,  $t_{max}$ ,  $AUC_{0-\infty}$ ,  $t_{1/2}$ ,  $Ae\%$ ,  $CL/F$ ,  $CL_R$ ,  $CL_{creatinine}$ ) for gabapentin were estimated by non-compartmental methods (SAS Pharmacokinetic Calculation System, version 3.1).

**Results**

The mean plasma concentration-time curves of gabapentin for the three different groups of children are shown in Figure 1.

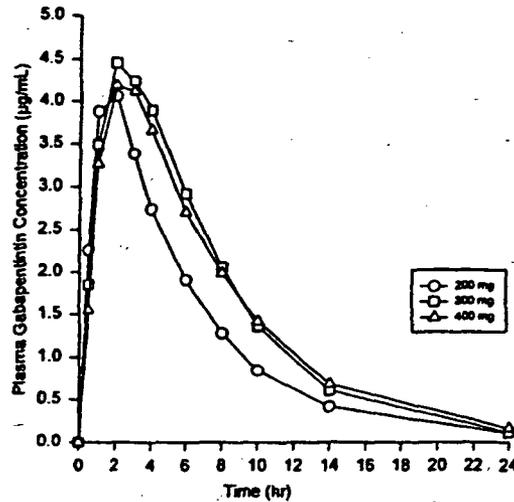


FIGURE 1. Mean plasma concentration-time curves of gabapentin after a single dose of 10 mg/kg gabapentin (Neurontin capsules) to healthy children (4-12 years old).

The pharmacokinetic parameters after the single dose (approximately 10 mg/kg) of gabapentin as a capsule are depicted in Table 1.

TABLE 1. Mean ± SD (range) pharmacokinetic parameters of gabapentin after a single oral dose administered to healthy children.

Parameter	Gabapentin Dose (Neurontin capsules)		
	200 mg	300 mg	400 mg
No. of subjects	7	8	9
Age (years)	4.9 ± 0.9 (4-6)	9.9 ± 1.6 (7-12)	11 ± 1.4 (8-12)
Weight (kg)#	20.5 ± 2.7 (16-24)	33.2 ± 3.1 (27-36)	44.5 ± 4.9 (38-52)
Dose (mg/kg)	9.8 ± 1.3 (8.3-12)	9.1 ± 0.9 (8.4-11)	9.1 ± 1.0 (7.7-11)
$C_{max}$ (µg/mL)	4.35 ± 1.37 (2.9-6.5)	4.55 ± 1.18 (2.6-6.9)	4.48 ± 1.23 (2.9-6.9)
$t_{max}$ (h)	1.4 ± 0.5 (1.0-2.0)	2.9 ± 0.6 (2.0-4.0)	2.7 ± 1.0 (1.0-4.0)
$AUC_{0-\infty}$ (µg·h/mL)	28.8 ± 12.1 (15.8-49.8)	37.7 ± 6.7 (28.4-47.5)	37.4 ± 11.5 (22.8-57.4)
$t_{1/2}$ (h)	5.40 ± 0.91 (4.1-6.7)	4.26 ± 0.42 (3.7-4.8)	4.87 ± 0.52 (4.0-5.7)
$Ae$ (%)*	30.7 ± 8.1 (14-37)	48.9 ± 15.6 (32-77)	37.0 ± 10.5 (22-53)
V/F (L/kg)	3.2 ± 1.8 (1.4-6.3)	1.5 ± 0.3 (1.1-2.0)	1.8 ± 0.5 (1.2-2.6)
CL/F (mL/min/kg)	6.51 ± 2.68 (3.96-10.8)	4.11 ± 0.64 (3.34-4.92)	4.30 ± 1.03 (3.05-5.70)
$CL_R$ (mL/min/kg)	1.97 ± 0.81 (1.13-3.62)	1.97 ± 0.36 (1.57-2.63)	1.57 ± 0.33 (1.06-1.95)
$CL_{creast}$ (mL/min)	54.7 ± 7.5 (44.5-65.3)	89.2 ± 12 (75.1-113.0)	91.9 ± 115.3 (76.4-124)

# Dose/kg based on actual weight of subjects; \* % unchanged drug excreted in urine

As shown Table 1, the AUC was about 20% lower, and oral clearance (CL/F) was about 35% higher in the youngest children (<25 kg body weight, aged 4-6 years) compared to the two other groups, although approximately equal doses per body weight were administered to all three groups of children. The time to reach  $C_{max}$  ( $t_{max}$ ) and half-life of gabapentin were similar across the three groups. However, the  $t_{max}$  was attained somewhat earlier in the youngest age group. The age was similar in the groups receiving 300 and 400 mg (mean age of 10 and 11 years, respectively), while the body weights differed between these two groups, as shown in Table 1.

Oral clearance (CL/F) correlated well to creatinine clearance, as shown in Figure 2.

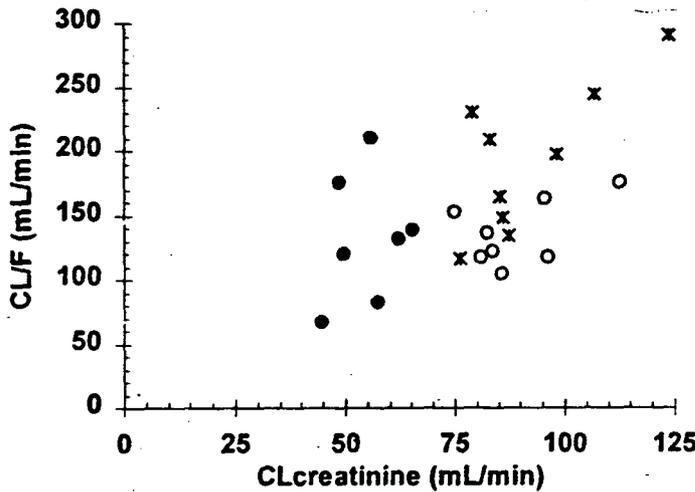


FIGURE 2. Oral gabapentin clearance (CL/F) vs. creatinine clearance after a single dose of approximately 10 mg/kg gabapentin (capsules) to healthy children weighing 16-25 kg (●), 26-36 kg (○), and 37-50 kg (\*), respectively.

Comments

The lower AUC resulting in a higher estimation of oral clearance in the youngest group of children compared to the two other groups indicates that the pharmacokinetics differs between the groups. Gabapentin is mainly eliminated via renal excretion of unchanged drug, nevertheless the renal clearance of gabapentin is similar across the groups. An explanation could be that the urine collection after dosing was not performed during an adequately long time period, which is reflected in the amount of drug recovered in urine, where only <50% of the dose was recovered. However, oral clearance of gabapentin correlated well with creatinine clearance of each subject (see Figure 2). It should be noted that the children receiving 300 mg (26-36 kg bodyweight) and 400 mg (37-50 kg) gabapentin were of similar age, the children participating in two groups had a mean age of 10 and 11 years, respectively.

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ON ORIGINAL

**Study # 2. Report RR-744-00378: A single dose study of gabapentin (CI-945) pharmacokinetics in healthy infants and children (protocol 945-296)**

(NDA 21-216, volume 4)

Objective

The aim of the study was to characterize single-dose pharmacokinetics of gabapentin in healthy infants and children (1-48 months of age).

Study Design and Demographics

This was an open-label, single dose study in 24 children. Twenty-six children (14F/12M, 21 Caucasian, 3 African American, 2 biracial) were enrolled in the study. The subjects were divided into four groups according to age,  $\geq 1$  and  $\leq 3$  months,  $> 3$  and  $\leq 12$  months,  $> 12$  and  $\leq 30$  months, and  $> 30$  and  $\leq 48$  months, respectively. A dose of 10 mg/kg gabapentin was administered as an oral solution (Neurontin<sup>®</sup> 50 mg/mL). The oral solution was administered in the morning after a 2-h fasting period.

Frequent blood samples were collected up to 24 h after drug administration.

Bioanalytical Method

ni

Pharmacokinetic Analysis

Pharmacokinetic parameters ( $C_{max}$ ,  $t_{max}$ ,  $AUC_{0-\infty}$ ,  $t_{1/2}$ ) for gabapentin were estimated by non-compartmental methods (WinNonlin Pro, version 2.1).

Results

Twenty-six children were enrolled in the study. However, one child (Subject no. 013) vomited 10 minutes after dosing, and was withdrawn from the study. This same child was re-enrolled at a later stage, as Subject no. 025. The adverse event (vomiting) was judged to not be drug-related.

It should be noted that the cut-off ranges of age for the different groups in the report do not match the actual mean values presented throughout the tables of the report. The sponsor has calculated means for the pharmacokinetic parameters and demographics as 'less than' (i.e.  $<$ ) the upper range, instead of 'the less than or equal to' (i.e.  $\leq$ ) the upper range for each age group, as stated in the report. The opposite holds true for the lower limits of cut-off ranges of age. The actual age limits used for comparisons can be found in Table 2.

NDA 21-216: Neurontin<sup>®</sup> (gabapentin oral solution)  
 NDA 20-235/S-015: Neurontin<sup>®</sup> capsules; NDA 20-882/S-002: Neurontin<sup>®</sup> tablets

The mean plasma concentration-time curves of gabapentin for the three different groups of children are shown in Figure 3.

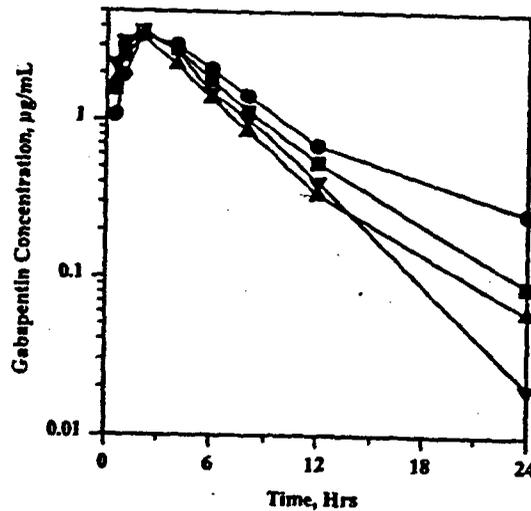


FIGURE 3. Mean plasma concentration-time curves (semi-logarithmic plot) of gabapentin after a single dose of 10 mg/kg gabapentin (Neurontin<sup>®</sup>) to healthy children aged  $\geq 1$  -  $< 3$  months ( $\bullet$ ),  $\geq 3$  -  $< 12$  months ( $\blacksquare$ ),  $\geq 12$  -  $< 30$  months ( $\blacktriangle$ ), and  $\geq 30$  -  $\leq 48$  months ( $\blacktriangledown$ ), respectively.

The pharmacokinetic parameters determined after the single dose (10 mg/kg) of gabapentin as an oral solution are depicted in Table 2.

TABLE 2. Mean  $\pm$  SD (range) pharmacokinetic parameters of gabapentin after a single oral dose (10 mg/kg) of an oral solution administered to healthy children.

Parameter	Age range (months)			
	$\geq 1$ - $< 3$	$\geq 3$ - $< 12$	$\geq 12$ - $< 30$	$\geq 30$ - $\leq 48$
No. of subjects	5	7	7	5
Age (months)	$1.2 \pm 0.45$ (1-2)	$7.0 \pm 3.3$ (3-11)	$18.4 \pm 6.0$ (12-28)	$36.0 \pm 7.0$ (30-47)
Weight (kg)	$4.92 \pm 1.08$ (3.6-6.6)	$7.81 \pm 1.53$ (6.0-9.8)	$11.33 \pm 1.46$ (9.7-13.9)	$13.92 \pm 1.86$ (11.9-16.9)
$C_{max}$ ( $\mu\text{g/mL}$ )	$3.56 \pm 1.61$ (1.6-5.2)	$3.93 \pm 1.76$ (1.9-7.0)	$3.43 \pm 0.81$ (2.3-4.4)	$3.87 \pm 0.69$ (3.2-4.8)
$t_{max}$ (h)	$2.80 \pm 1.10$ (2.0-4.0)	$1.95 \pm 1.01$ (1.0-4.0)	$2.00 \pm 0$ (2.0-2.0)	$2.42 \pm 0.88$ (2.0-4.0)
$AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{h/mL}$ )	$31.1 \pm 9.5$ (21.9-45.9)	$26.5 \pm 14.0$ (14.6-55.4)	$20.9 \pm 4.3$ (13.8-25.0)	$23.8 \pm 4.53$ (17.0-28.1)
$CL/F$ ( $\text{mL/min/kg}$ )	$5.73 \pm 1.56$ (3.6-7.6)	$7.45 \pm 2.78$ (3.0-11.4)	$8.33 \pm 2.02$ (6.7-12.1)	$7.24 \pm 1.58$ (5.9-9.8)
$V/F$ ( $\text{L/kg}$ )	$2.6 \pm 1.1$ (1.5-4.2)	$3.2 \pm 2.1$ (1.1-6.2)	$2.5 \pm 0.8$ (1.5-3.5)	$1.8 \pm 0.1$ (1.6-1.8)
$t_{1/2}$ (h)	$5.15 \pm 1.39$ (2.9-6.4)	$4.75 \pm 2.22$ (2.3-9.2)	$3.39 \pm 0.75$ (2.5-4.3)	$2.92 \pm 0.70$ (1.8-3.6)
$CL_{creatinine}$ ( $\text{mL/min}$ )	$13.64 \pm 4.88$ (7.1-19.9)	$27.21 \pm 7.47$ (19.5-41.3)	$42.7 \pm 8.64$ (33.5-59.0)	$51.08 \pm 19.82$ (35.2-85.6)

As shown in Table 2, the time to reach  $C_{max}$  ( $t_{max}$ ) and half-life of gabapentin were similar across the four age groups. The oral clearance (CL/F) did not show a strong correlation to age, after adjustment for bodyweight was made, as shown in Figure 4.

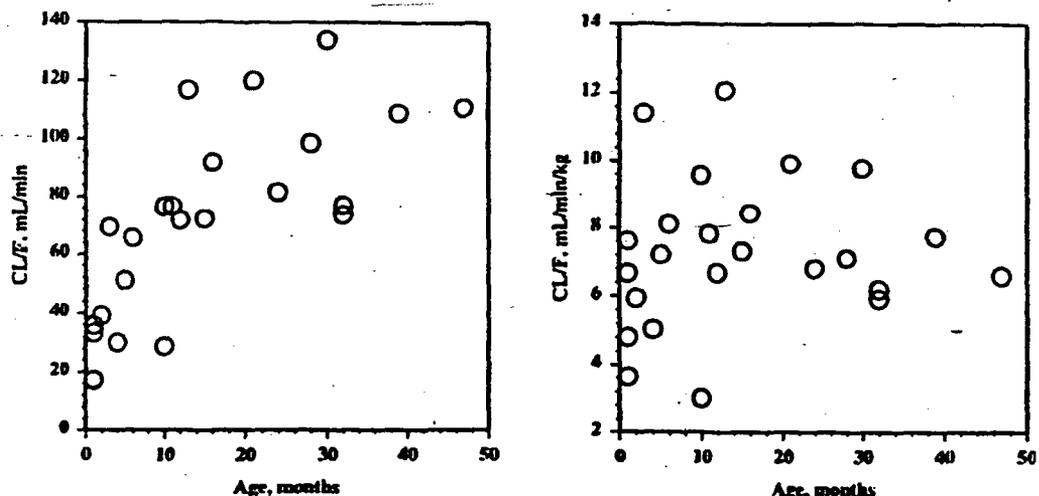


FIGURE 4. Oral gabapentin clearance (CL/F) vs. age after a single dose of 10 mg/kg gabapentin oral solution (Neurontin<sup>®</sup>) to healthy children aged 1-48 months. LEFT PANEL: Unadjusted CL/F RIGHT PANEL: CL/F corrected for body weight

Oral clearance (CL/F) correlated well to creatinine clearance, as shown in Figure 5.

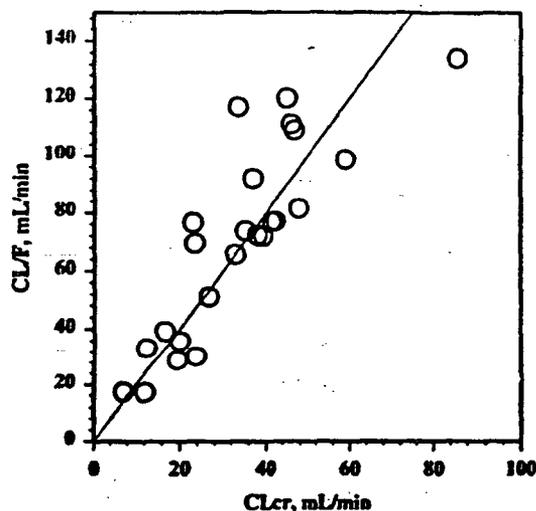


FIGURE 5. Oral gabapentin clearance (CL/F) vs. creatinine clearance (CLcr) after a single dose of 10 mg/kg gabapentin (Neurontin<sup>®</sup>) to healthy children aged 1-48 months.  
( $CL/F = 14.6 + 1.66 \times CLcr$ ,  $r = 0.846$ )

#### Comments

The sponsor concludes that the pharmacokinetics is similar over the studied age range of children, i.e. 1-48 months. However, there is a tendency of lower oral clearance in the children aged 1-2 months, also after correction for bodyweight, as shown in Figure 4. The oral clearance of gabapentin shows a good correlation to creatinine clearance, which would be expected, since the drug is mainly eliminated via renal excretion.

### Overall Comments for Studies #1 and #2.

Creatinine clearance was shown to be a good predictor of the oral clearance of gabapentin, as shown in Figure 6 below.

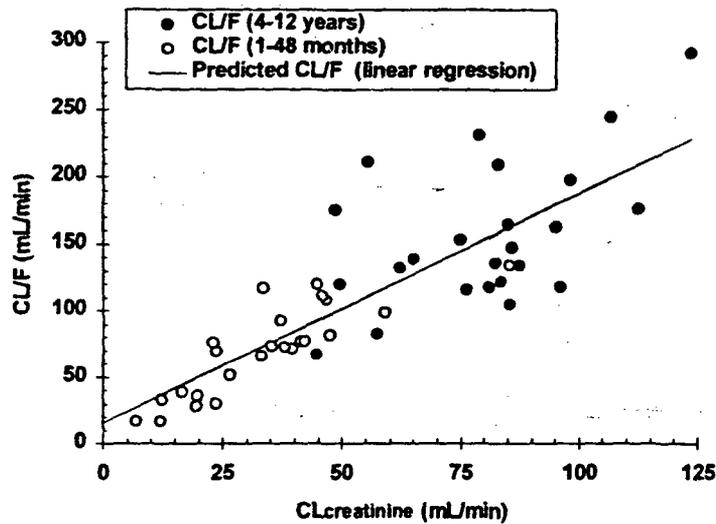


FIGURE 6. Oral gabapentin clearance (CL/F) vs. creatinine clearance (CLcr) after a single dose of approximately 10 mg/kg gabapentin to healthy children (oral solution <4 years old; capsules age 4-12 years). The linear regression was described by  $CL/F = 15.7 + 1.72 \times CLcr$ ;  $r = 0.832$

The volume of distribution (V/F) and oral clearance (CL/F), after adjustment for body weight, in relation to age are shown in Figure 7. There was a tendency of higher volumes of distribution in the younger children, however the coefficient of variation was large (>50%), and there is no clear trend in the data.

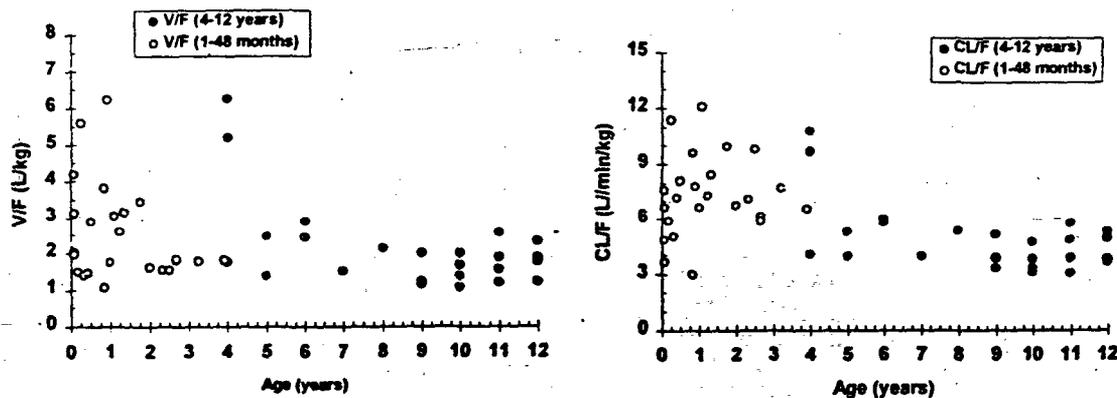


FIGURE 7. Volume of distribution (V/F per kg; left panel) and oral gabapentin clearance (CL/F per kg; right panel) vs. age after a single dose of approximately 10 mg/kg gabapentin to healthy children (oral solution <4 years old; capsules age 4-12 years).

The overall average oral clearance was  $4.9 \pm 1.9$  mL/min/kg and  $7.3 \pm 2.2$  mL/min/kg for children 4-12 years old, and 1-48 months old, respectively. The corresponding values for volume of distribution (V/F) were  $2.1 \pm 1.2$  L/kg and  $2.6 \pm 1.3$  L/kg for the two groups. The overall oral clearance was approximately 30% lower in children older than 4 years.

The sponsor has proposed the following label text based on the results from Studies #1 and #2 (Appendix 2, page 49):

*"Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2 to 3 hours postdose. In general, pediatric subjects between 1 month and <5 years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in the younger children. Apparent oral clearance of gabapentin was directly proportional to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied."*

The sponsor's proposed label text regarding Study #1 and Study #2 should be revised according to section 'LABELING REVISIONS', on page 15 in this review.

### **Population pharmacokinetic (PPK) analysis summary**

The full pharmacometric review by Dr. E Mishina is found in Appendix 1 (page 17).

#### Data used in the PPK analysis

Data were collected in two studies in healthy pediatric subjects (Studies #1 and #2) and in five efficacy/safety studies in pediatric patients, and pooled for the population analysis. The study design, study population, and timing of blood samples varied between the seven studies. Gabapentin was administered as a single dose or as multiple doses given as either capsules or ~~tablets~~ depending on the age of the child. In the multiple-dose studies, the intended doses ranged from 10 to 60 mg/kg/day given as a TID regimen at 8 a.m., 2 p.m., and 8 p.m. The investigators were asked to document the date and time of the most recent dose and of sample collection. The five efficacy/safety studies in pediatric patients were the following:

*Protocol 945-94:* A double-blind study in pediatric patients with benign childhood epilepsy with centrotemporal spikes (BECTS).

*Protocol 945-95:* An extended open-label gabapentin (CI-945) pediatric monotherapy trial following a double-blind study (Protocol 945-094) in pediatric patients with benign childhood epilepsy with centrotemporal spikes (BECTS).

*Protocol 945-86/186:* A double-blind parallel group comparison of (gabapentin versus placebo as add-on therapy for epilepsy in children. Protocol 945-86 was used for sites in the UK, while Protocol 945-186 was used for all other sites in Europe, South Africa, and the US.

*Protocol 945-305/405:* Gabapentin pediatric add-on trial: A randomized, double blind, placebo-controlled, parallel group, multi-center study in patients with partial seizures.

Protocol 945-305 was used for sites in the US and Canada while Protocol 945-405 was used for all other international sites.

*Protocol 945-301/401:* Open-label, safety study of gabapentin (CI-945) as adjunct therapy in children aged 1 month through 4 years with seizures uncontrolled by current anticonvulsant drugs: Protocol 945-301 was used for sites in the US and Canada while Protocol 945-401 was used for all other international sites.

In the full data set used for the population analysis, 422 gabapentin concentrations were collected from healthy subjects and combined with 317 gabapentin concentrations obtained at steady state at unspecified timed intervals from 205 pediatric patients in the clinical efficacy/safety studies. The distribution of patients and healthy subjects were well balanced by age and gender across the studies. The applicant removed several observations from the data set due to missing or incorrect dosing information. A total of 1366 gabapentin concentrations were available for the data analysis of which 739 (54%) were actually used. The applicant did not provide a full explanation of particular data withdrawal from the data sets. In response on the FDA request for the explanation,

the applicant reported that from studies 945-86/186 the data were omitted due to improper registration of the time of the last dose as well as the time of plasma samples. The data from study 945-95 were omitted when the demographic characteristics were not recorded. Therefore, these data were not examined for the statistical criteria for the outliers, as described in *Population Pharmacokinetics, Guidance for the Industry*. The omitted samples could not be used for the incorporation into the population pharmacokinetic model.

#### Population model

The initial model for the healthy subjects was a one-compartment model with absorption and lag-time in terms of clearance and volume of distribution. A two-compartment model was evaluated as well but without success. The applicant finalized the model for healthy subjects with the proportional influence of creatinine clearance on clearance and the same of body weight on volume of distribution. The error model was chosen as a combined additive and proportional model. Residual variability was described with a proportional coefficient of variability of 9.39% and a standard deviation for the additive term of 0.105  $\mu\text{g/mL}$ .

In the final data analysis, the sponsor included 739 gabapentin plasma concentration samples from 253 subjects. The limit of quantitation for the safety and efficacy studies ranged between  $\text{---}$ . The doses ranged from 10 to 66 mg/kg/day, and the time of post-dose collection ranged from 0.08 to 21.3 hrs. The healthy subjects' data were obtained on the first day and the patients' data were obtained (at steady state, TID) on days 2-4.

The sponsor repeated the steps for the initial model building with the combined data set. Although the variability in the combined data set was larger, the model built for the healthy subjects was acceptable for the total population as well.

Then the sponsor identified the basic structural model by incorporating covariates one at a time in the model and evaluated if the added covariate would explain inter-subject variability in the pharmacokinetic parameters. The most important covariates were race, formulation, use of phenytoin on CL/F, and study population on V/F. These covariates were reevaluated. The applicant then removed each of the important covariates from the model by fixing the coefficient to zero. At this step proper adjustment of the p-value for the multiple comparison was performed.

#### Results

Clearance values normalized by body weight in small children (under 5 years old) were higher and more variable than in the group of children 5-13 years old, as shown in Figure 8.

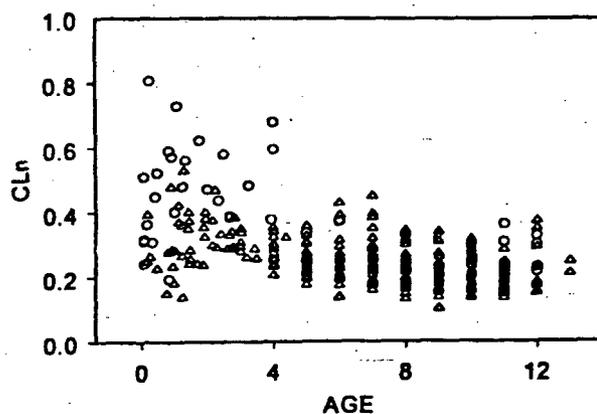


FIGURE 8. Clearance normalized by body weight vs. age. Triangles denote patient data, and circles denote data from the healthy subjects.

On average, the post-hoc estimates of normalized CL/F were 30% larger for the children younger than 5 years old. This finding is the basis for the 30% of dose adjustment proposed for this group of children. Additionally, non-compartmental data analysis of all subjects indicates that a 50% higher dose is necessary to achieve the same exposure in small children as in the age group of 5-12 years old. Therefore, dose adjustment was recommended from 30 to 40 mg/kg/day in children less than 5 years old. This dose adjustment is properly included in the proposed label text.

The estimate of V/F was related to the body weight. This relationship was different for the populations of healthy subjects and patients with the slope more than two-fold larger in patients. In the plot of the volume of distribution normalized by body weight, as shown in Figure 9, the difference between populations is even more pronounced. The applicant speculated that the possible reasons for this discrepancy may be explained by the difference in the dosing (single vs. multiple), sample collection (intense vs. sparse), population (healthy vs. patients) and compliance. The real reason for this discrepancy is unknown; however, each of the listed possibilities may contribute to it.

### Volume Normalized by WGT vs WGT

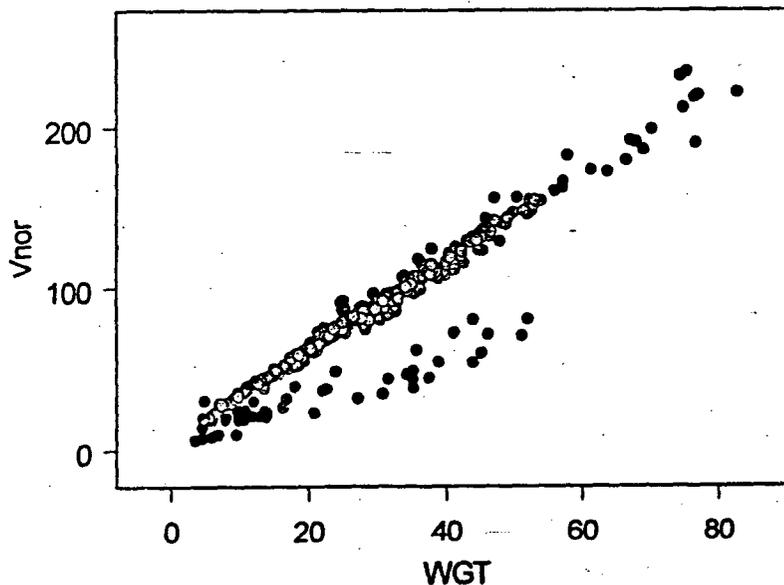


FIGURE 9. Volume of distribution (normalized for body weight) of each individual patient vs. body weight. Light color of circles denote data from patients, dark color of circles denote data from healthy subjects.

There was a trend towards a dependence of CL and volume of distribution on the population (healthy subjects and patients). However, a reanalysis performed by the FDA, without accounting for the population, shows that this difference was not pronounced, i.e. this trend is not considered to be of major importance.

### Conclusions

- The applicant omitted about 46% of the originally reported data due to improper data records (unreported time of last dose, unreported time of the plasma samples, absence of demographic data). Based on the data, which were appropriately collected for the pharmacokinetic analysis, the applicant adequately performed the population analysis of the combined pediatric data from 7 studies: two studies with the rich data from healthy subjects and 5 studies with sparse sampling data obtained from the patients. Overall, the estimation of pharmacokinetic parameter values seems reasonable. This data analysis adds value to the corrections of the label text.
- Population data analysis showed that the influence of body surface area, gender, height, formulation, disease (population), co-administration of phenytoin, phenobarbital, valproic acid, carbamazepine, vigabatrin on clearance was statistically insignificant. The covariates did not affect the estimation of the rate of gabapentin absorption and the lag-time values.
- Population data analysis showed that the influence of age, gender, race, formulation on volume of distribution of gabapentin was statistically insignificant. The covariates did not affect the estimation of the rate of gabapentin absorption and the lag-time values.
- Gabapentin oral clearance was directly related to creatinine clearance, which was expected because gabapentin is exclusively eliminated by the kidney.
- Gabapentin clearance normalized by body weight was on average 30% higher in the group of children 5 years and younger. In the label, the dose for the children younger than 5 years old was adequately adjusted to 40 mg/kg/day.
- In the final model for the combined data set, inter-subject variability was about 30% for both CL/F and V/F, 43% for  $k_a$  and 79% for  $t_{lag}$ . In healthy subjects, the residual variability (proportional: CV=10%, additive: 0.25  $\mu\text{g/mL}$ ) was much smaller than the same for the pediatric patients (proportional: CV=25%, additive: 1.32  $\mu\text{g/mL}$ ). This difference in variability was explained by the difference in the assay concentration ranges for these populations.

For further information regarding the population pharmacokinetic analysis, see Appendix 1.

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**LABELING REVISIONS**

The sponsor has provided efficacy data for children aged 3 years and older. Since only safety and pharmacokinetic information is available for children below the age of 3, any information regarding children <3 years old will not be included in the label text according to the Medical Division (HFD-120).

The sponsor is requested to revise the section CLINICAL PHARMACOLOGY - Pharmacokinetics and Drug Metabolism - Special Populations –subsections ‘Renal impairment’ and ‘Pediatric’, and also the DOSAGE AND ADMINISTRATION section as follows (strike through text = deleted text; underlined text = revised text):

**Special Populations: Patients With Renal Insufficiency:** *The first paragraph will be kept according to the sponsor’s proposal (see Appendix 2, page 48 of this review)*

Dosage adjustment in adult patients with compromised renal function is necessary (see DOSAGE AND ADMINISTRATION). Pediatric patients with renal insufficiency have not been studied.

*Hemodialysis: The first paragraph will be kept according to the sponsor’s proposal (see Appendix 2, page 49 of this review)*

**RECOMMENDATION**

From a pharmacokinetic point of view, this NDA for the treatment of partial seizures in pediatric patients is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

The sponsor is requested to incorporate all labeling changes. Please forward the labeling changes to the sponsor.

Maria Sunzel, Ph.D., (primary reviewer)

*Sept 6, 2000* *MS*

Elena Mishina, Ph.D., (pharmacometrics reviewer)

*MS* *9/6/00*

RD/FT initialed by Emmanuel O. Fadiran, Ph.D.,

*MS* *9/6/2000*

Division of Pharmaceutical Evaluation I,  
Office of Clinical Pharmacology and Biopharmaceutics

c.c.: NDA 21-216, HFD-120, HFD-860 (Mehta, Fadiran, Mishina, Sunzel), HFD-340 (Viswanathan), Central Document Room (Biopharm files) and FOI files (HFD-19)

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**Appendix 1: Pharmacometric review of the population pharmacokinetic analysis**

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**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW  
PHARMACOMETRICS REVIEW**

**NDA 21-216**

**Submission Dates: February 28, September 1, 2000**

**Drug Name:** NEURONTIN (gabapentin)  
**Formulation:** solution  
**Applicant:** Parke-Davis  
**Consult:** Report: "Population Pharmacokinetics of Gabapentin in Infants and Children"  
**Pharmacometrics Specialist:** Elena V. Mishina, Ph.D.

**Preamble/Background:**

Gabapentin (Neurontin®) is a novel anticonvulsant approved for adult patients (12 years of age and older) as adjunctive therapy in the treatment of partial seizures. NDA 20-235 (capsule) and NDA 20-882 (tablet) were approved and have the same Package Insert. NDA 21-129, submitted on April 30, 1999 was pending on the day of submission of this report. Gabapentin in pediatric patients was studied with both capsule and formulations, and pediatrics data were summarized together. The applicant intends to use a common Package insert for all three NDAs (20-235, 20-882, and 21-129).

In order to include in the Package Insert the information on the gabapentin pharmacokinetics in pediatric population, the sponsor performed the pharmacokinetic study in healthy infants and children (age 1 month to 12 years). Gabapentin pharmacokinetics at steady state in the target patient population was characterized based on the sparse samples obtained in 5 different clinical efficacy/safety studies in infants and children. The report summarizes the results of the population pharmacokinetic analysis combining concentration data from these studies.

The objectives of these data analysis were  
to determine gabapentin pharmacokinetic parameters including inter-subject variability,  
to identify the clinical factors that are important determinants of the inter-subject variability.

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA). Its mechanism of action is unknown. Gabapentin does not interact with the GABA receptor, is not converted to GABA or a GABA agonist, and is not an inhibitor of GABA uptake or degradation. In clinical studies with gabapentin in adults the sponsor has shown that the drug is well-tolerated, has a wide therapeutic margin, demonstrates a high degree of efficacy, and does not result in relevant drug or food interactions, particularly with other antiepileptic drugs. Gabapentin is eliminated exclusively via glomerular filtration, and the elimination rate is dependent on renal clearance. Following oral administration of gabapentin in adults, peak plasma concentrations are observed approximately 3 hours post-dose and the elimination half-life, independent of dose,

averages between 5 and 7 hours. Food has no effect on the rate and extent of absorption of gabapentin. The absolute bioavailability of gabapentin from 300 mg capsule and solution formulations is approximately 60%. The extent of gabapentin absorption is not dose-proportional with a less than proportional increase in the area under the curve (AUC) with increasing doses.

#### **Methods:**

##### ***Study Design:***

Data collected from 2 studies in healthy pediatric subjects and 5 efficacy/safety studies were pooled for the population analysis. The study design, study population, and timing of blood samples varied between the 7 different clinical studies. Gabapentin was administered as a single dose or as multiple doses given as either capsules or ~~\_\_\_\_\_~~ depending on the age of the child. In the multiple-dose studies, the intended doses ranged from 10 to 60 mg/kg/day given as a TID regimen at 8:00, 14:00, and 20:00. The investigators were asked to document the date and time of the most recent dose and of sample collection. List of the studies is following:

##### ***Studies in Healthy Pediatric Subjects:***

Protocol 945-202: A single-dose study of Neurontin (Gabapentin; CI-945) pharmacokinetics in healthy pediatric subjects.

Protocol 945-296: A single-dose study of gabapentin syrup (CI-945) pharmacokinetics in healthy infants and children.

##### ***Efficacy and Safety Studies in Pediatric Patients***

Protocol 945-94: A double-blind study in pediatric patients with benign childhood epilepsy with centrotemporal spikes (BECTS).

Protocol 945-95: An extended open-label gabapentin (CI-945) pediatric monotherapy trial following a double-blind study (Protocol 945-094) in pediatric patients with benign childhood epilepsy with centrotemporal spikes (BECTS).

Protocol 945-86/186: A double-blind parallel group comparison of (gabapentin versus placebo as add-on therapy for epilepsy in children. Protocol 945-86 was used for sites in the United Kingdom while Protocol 945-186 was used for all other sites in Europe, South Africa, and the US.

Protocol 945-305/405: Gabapentin pediatric add-on trial: A randomized, double-blind, placebo-controlled, parallel-group, multi-center study in patients with partial seizures. Protocol 945-305 was used for sites in the US and Canada while Protocol 945-405 was used for all other international sites.

Protocol 945-301/401: Open-label, safety study of gabapentin (CI-945) as adjunct therapy in children aged 1 month through 4 years with seizures uncontrolled by current anticonvulsant drugs. Protocol 945-301 was used for sites in the US and Canada while Protocol 945-401 was used for all other international sites.

Details of the study designs are listed in the Table 1, Appendix A.

**Assay Method:**

analyzed plasma samples for gabapentin concentrations using The standard curves

**Data Analysis:**

Two data sets were created for NONMEM analysis, set 1 contained data from healthy subjects, and set 2 combined all concentration data. The data sets included subject demographic and physiologic characteristics and use by the patients of the most common antiepileptic medications. The exact time of sample collection was not specified in the different efficacy/safety study protocols. The sample was obtained at any time during the patient's visit to the clinic, with the exact time of collection of the sample as well as the time of the last dose recorded. From this information, the exact elapsed time since the last dose was derived. In these studies with TID dosing regimen with doses at 8:00, 14:00, and 20:00 (clock time), steady state was assumed to be achieved prior to plasma sample collection. Steady-state doses on the day prior to that sample were imputed in the dataset. For samples collected after a morning or an afternoon dose, additional dosing events representing these doses on the day of the sample collection were included in the dataset. The exact elapsed time of sample collected was adjusted according to the dose time of 0, 6, or 12 hour. All doses were included as different dose events. Age, weight, height, serum creatinine and use of concomitant medications were recorded at the time of first visit and then updated on each visit for the clinical efficacy studies.

Body surface area (BSA) was calculated as

$$BSA(m^2) = WT(kg)^{0.425} \cdot HT(cm)^{0.725} \cdot 71.84$$

Creatinine clearance normalized by 1.73 m<sup>2</sup> (nCrCL) was calculated from serum creatinine (SCr) as follows

or infants <1 year:

$$nCrCL(mL/min/1.73 m^2) = 0.45 \cdot HT(cm) / SCr$$

for children 1 year and older:

$$nCrCL(mL/min/1.73 m^2) = 0.55 \cdot HT(cm) / SCr$$

Creatinine clearance then was calculated for the individual using his (her) BSA.

If the covariate was not recorded at the time of a visit, a missing value was replaced with either the prior measured or the average value for this subject. Variables included in the data are listed in Table 2, Appendix A.

**Model Building:**

The applicant performed population data analysis with NONMEM Version V. Firstly, Phase I studies data in healthy pediatric subjects were analyzed in order to

- Identify a basic pharmacokinetic model (no covariates added), with estimates of inter-subject and residual variability
- Obtain individual Bayesian estimates of pharmacokinetic parameters for each patient using the POSTHOC option;
- Identify important covariates using a generalized additive model (GAM) approach and plots of posthoc pharmacokinetic parameter estimates versus covariates;
- Add each significant covariate in the NONMEM model and retest the full model.

The applicant then repeated each step of the model building used with the healthy pediatric subjects for the combined dataset, tested the additional covariates, one at a time in NONMEM, added each significant covariate in NONMEM to obtain the full model. The full model was tested to identify the final model.

**Criteria for Model Building:**

The goodness of fit of different models to the data was evaluated using the following criteria: change in the objective function, decreases in both inter-individual variability and residual variability, as well as visual inspection of different scatter plots:

- predicted versus observed concentrations (PRED vs. DV),
- individual predicted versus observed concentrations (IPRED vs. DV),
- weighted residuals versus predicted concentrations (WRES vs. PRED),
- individual weighted residuals versus individual predicted concentrations (IWRES vs. PRED).

These criteria were used only when the minimization step was successful and standard errors of parameter estimates were obtained using the covariance step. The difference in minimum objective function (MOF) values between 2 hierarchical models has an approximate  $\chi^2$  probability distribution with the number of degrees of freedom for the  $\chi^2$  distribution equal to the number of parameters added. Any decrease of >6.6 in the objective function indicates that a proposed model with one additional parameter is better than the reduced reference model ( $p < 0.01$ ).

Initial model for healthy children was one-compartmental PK model with first order absorption. Inter-subject variability was assumed to be distributed log-normally and modeled as proportional term:

$$CL/F = 9 \cdot e^{\eta}$$

The 95% confidence intervals (CI) for the parameter estimates were calculated as

$$CI = 9 \pm 2 \cdot SE$$

where SE is standard error obtained by NONMEM.

The applicant used coefficient 2 as an approximation of the value of 1.96 obtained from the  $\chi^2$  probability distribution with the increase of degree of freedom by one. The

of inter-subject variability ( $\eta$ ) was provided as percent coefficient of variation (%CV), this was calculated as  $(\sqrt{\omega^2}) \cdot 100$ . The 95% CI for inter-subject variability were calculated as  $(\sqrt{\omega^2} \pm 2 \cdot SE) \cdot 100$ . Residual variability was initially modeled as a proportional residual error model:

$$Y = F \cdot (1 + \epsilon)$$

where Y is the observed plasma concentration and F is the predicted plasma concentration based on the pharmacokinetic model; the random variable  $\epsilon$  that defined residual variability had a normal probability distribution with mean 0 and variance denoted as  $\sigma^2$ . Residual variability was also provided as %CV, as explained above. Alternatively, a combined additive/proportional error model was tested during model building as described below:

$$Y = F + F \cdot \epsilon_1 + \epsilon_2,$$

where Y is the observed plasma concentration, F is the predicted plasma concentration based on the pharmacokinetic model,  $\epsilon_1$ , is the proportional error component of the residual variability, and  $\epsilon_2$  is the additive error component of the residual variability.

#### *Covariates*

For the basic pharmacokinetic model for healthy pediatric subjects, posthoc estimates of each pharmacokinetic parameter were obtained. Then the applicant performed a multiple regression analysis to screen for important covariates. Significant covariates were identified based on the Akaike Information Criterion (AIC). Covariates that produced a statistically significant ( $p < 0.01$ ) decrease in the NONMEM objective function ( $> 6.6$  units) were sequentially added to the model. For the analysis with the combined data, the model used in the healthy pediatric subjects was tested. Each covariate was then tested one at a time for statistical significance sequentially. Continuous covariates were added to the model as

$$\text{TrueParameter} = \Theta_1 + \Theta_2 \cdot (\text{Covariate} - \text{Median})$$

and dichotomic covariates were modeled as

$$\text{TrueParameter} = \Theta_1 \cdot (1 - \Theta_2 \cdot \text{Covariate})$$

An arbitrary number of 20 subjects was selected as a minimum number of subjects required for that covariate to be tested.

When all significant covariates were included in the model, the applicant further tested this full model by elimination each of parameter one at a time fixing their values to zero. The p value for statistical significance was adjusted for multiple comparisons ( $p < 0.001$ ). The final model included only those parameters that produced an increase in the objective function of  $> 10.8$  for one degree of freedom when they were excluded.

*Model Validation:*

The applicant did not perform an actual model validation by the splitting of full data set for index and validation sets. The applicant used for validation of the basic model built using the rich data file for healthy subjects the combined data set for all pediatric patients (sparse sampling) and subjects. These data sets have different statistical quality. Therefore, the biases in the final model could be expected.

**Results:**

*Data description:*

In full data set 422 gabapentin concentrations were collected from healthy subjects and combined with 317 gabapentin concentrations obtained at steady state at unspecified timed intervals from 205 pediatric patients in the clinical efficacy/safety studies. A summary of dosing information, sampling collection times and gabapentin concentration ranges for all studies are shown in Table 3, Appendix A. Demographic characteristics by study are shown in Table 4, Appendix A. The distribution of patients and healthy subjects were well balanced by age and gender across the studies. The applicant removed several observations from the data set due to missing or incorrect dosing information. A total of 1366 gabapentin concentrations were available for the data analysis of which 739 (54%) were actually used. The applicant did not provide the explanation of particular data withdrawal from the data set. In response on the FDA request for the explanation (see Appendix A, page 45), the applicant reported that from studies 86-186 the data were omitted due to improper registration of the time of the last dose as well as the time of plasma samples. The data from study 95 were omitted when the demographic characteristics were not recorded. Therefore, these data were not examined for the statistical criteria for the outliers (Population Pharmacokinetics, Guidance for the Industry), the omitted samples could not be used for the incorporation into the population pharmacokinetic model.

The applicant provided only some of the plots used for the model diagnostics.

FDA re-ran the final proposed by the applicant model for the healthy subjects. The NONMEM output was very similar to the one submitted by the applicant. FDA graphically (S-PLUS 2000) assessed its goodness of fit. The observed (circles), individual predicted (solid lines) and population predicted (dashed lines) gabapentin plasma concentrations vs. time data are shown in Figure 1. The results are obtained from the posthoc file provided by the applicant. The proposed model describes the data well. The initial model for the healthy subjects was a one-compartment model with absorption and lag-time in terms of clearance and volume of distribution. A two-compartment model was evaluated as well but without success. The applicant finalized the model for healthy subjects with the proportional influence of creatinine clearance on clearance and the same of body weight on volume of distribution. The error model was chosen as a combined additive and proportional model. Residual variability was described with a proportional coefficient of variation of 9.39% and a standard deviation for the additive term of 0.105

mcg/mL. Table 7, Appendix A, lists the parameter estimates and confidence intervals for the healthy patients.

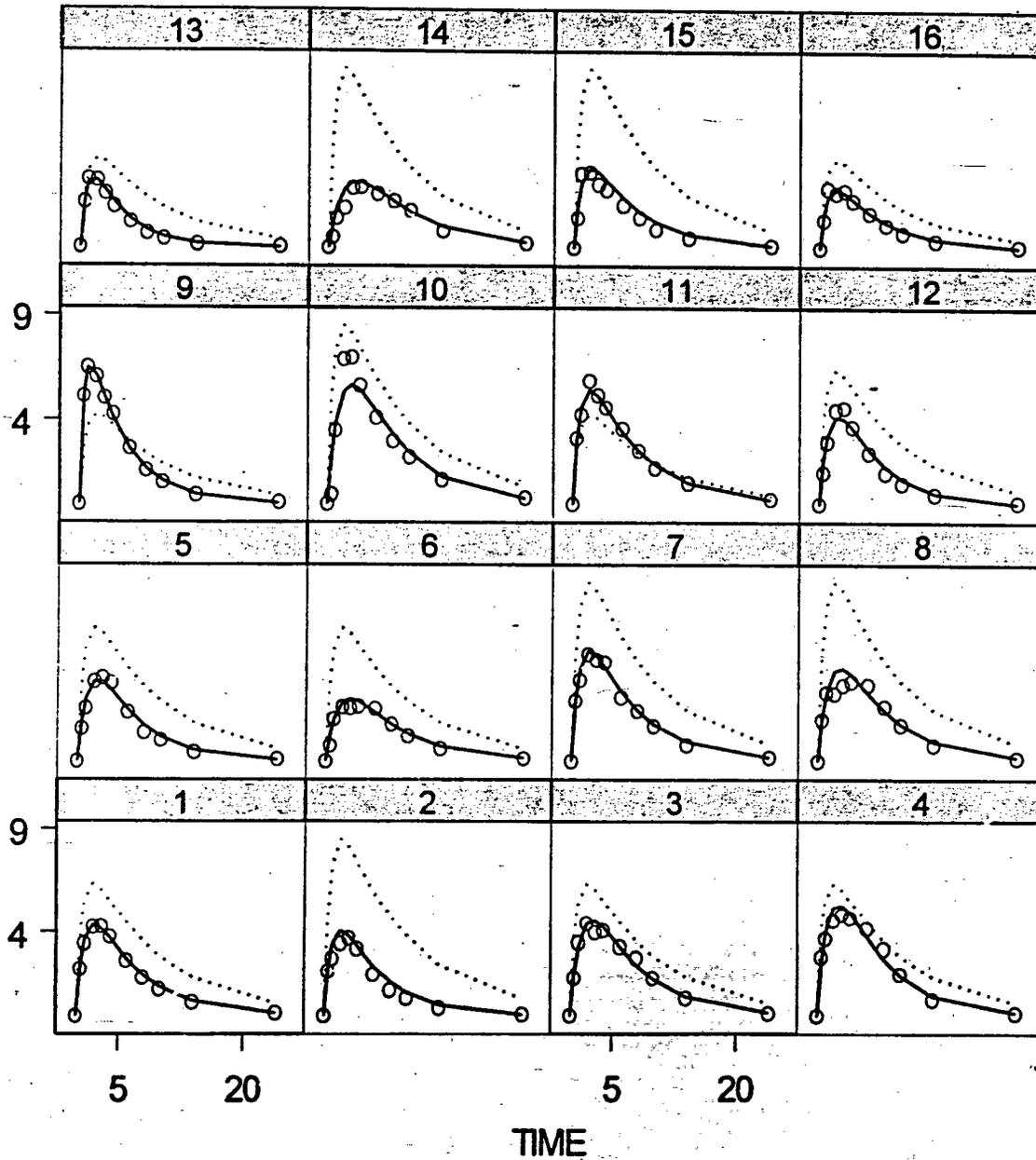


Figure 1. Gabapentin plasma concentration vs. time profiles. Circles are the observed data, solid lines are the individual predicted plasma concentrations and dashed lines are the population predicted plasma concentrations.

FDA plotted the pharmacokinetic parameters (CL, V, ka, tlag) vs. ETAs to find if any trend would be seen. No trend was found, Figure 2.

## PK Parameters vs ETAs

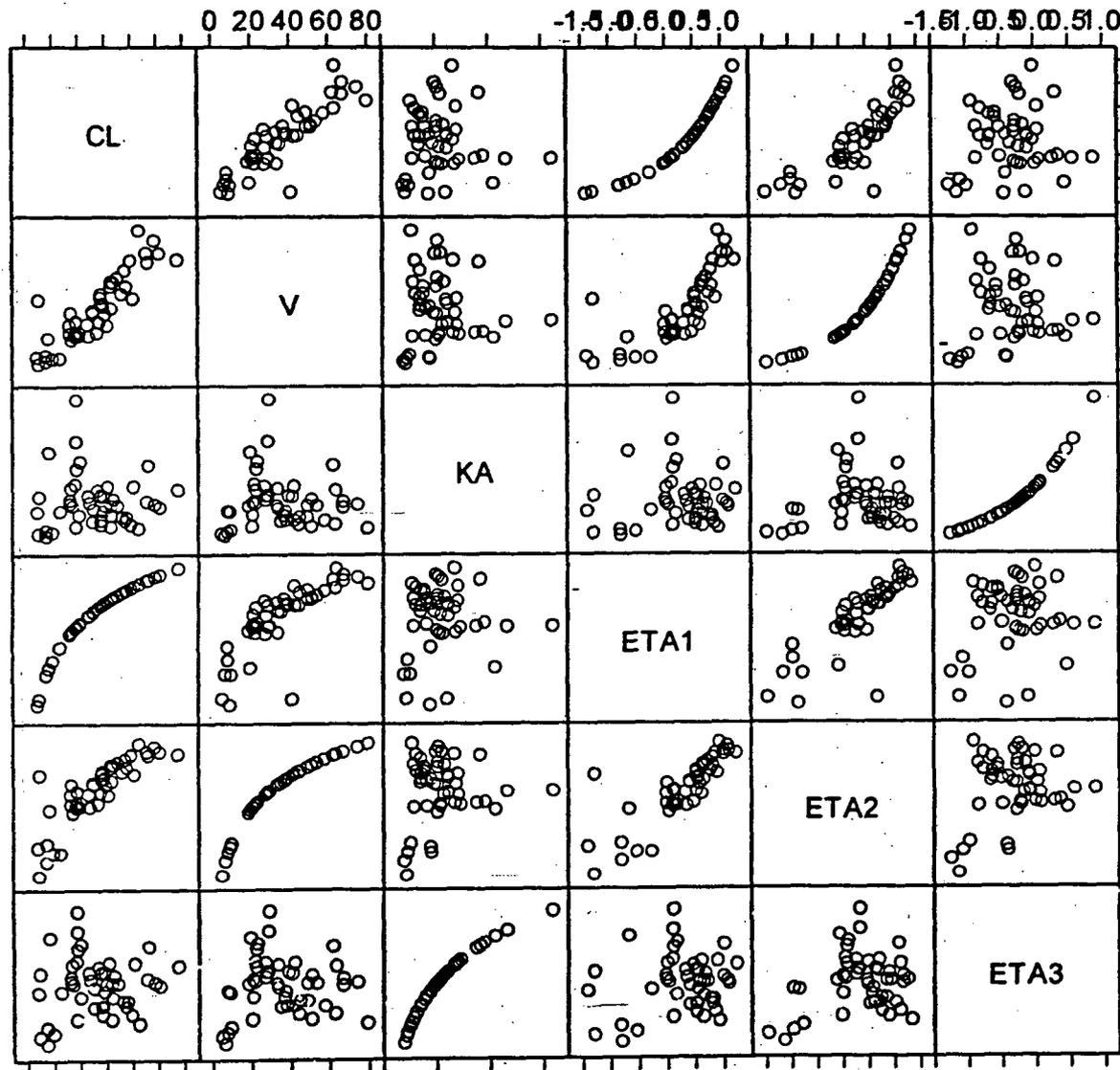


Figure 2. PK parameters for healthy subjects vs. ETAs

The plot of WRES vs. PRED (FDA, Figure 3) show the equal distribution of weighted residuals along the value for the all range of predicted gabapentin plasma concentrations.

## PK Parameters vs Covariates

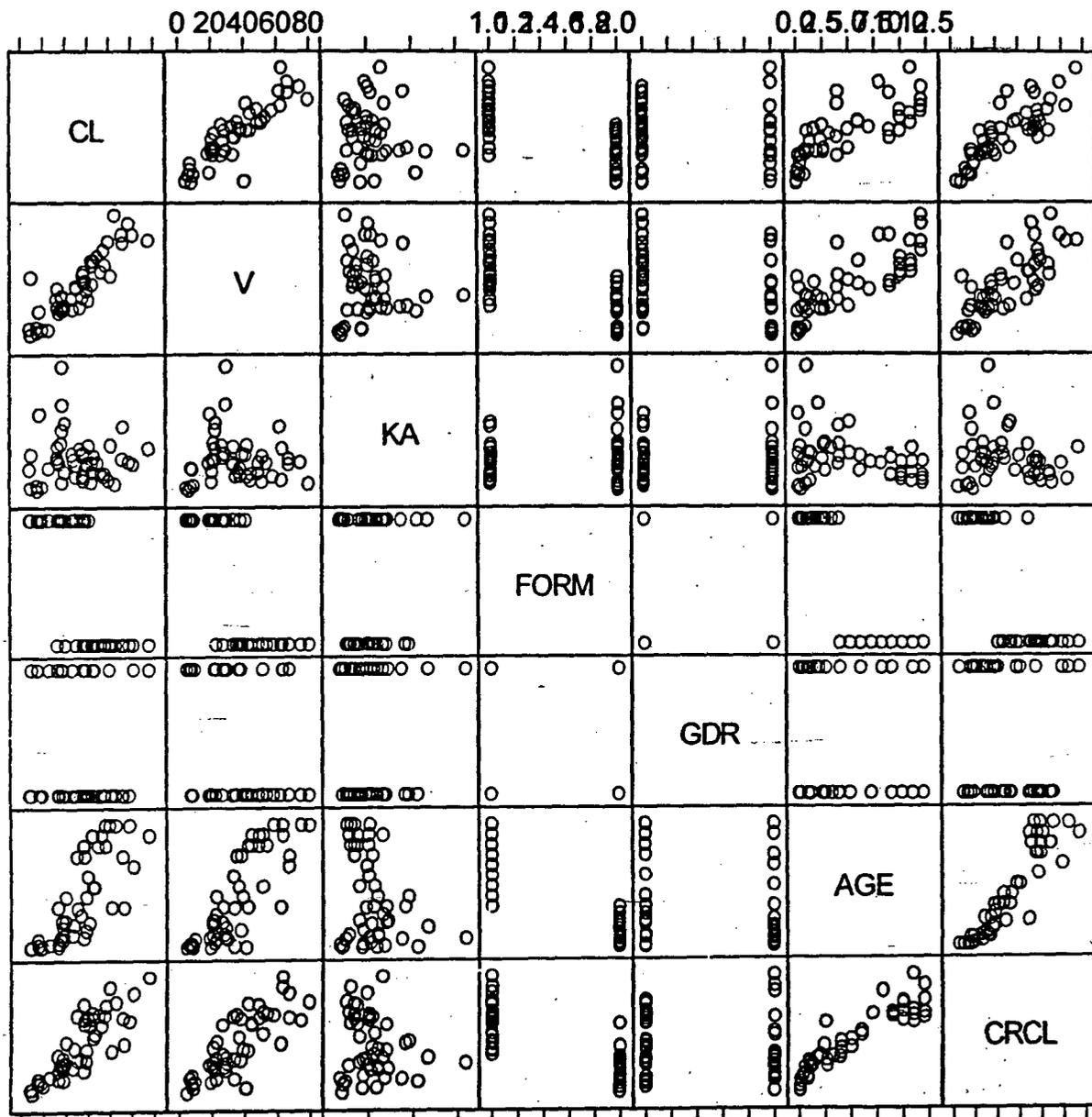


Figure 3. PK parameters for healthy subjects vs. covariates (FORM=formulation, GDR=gender, all other abbreviations are standard abbreviations).

Therefore, the applicant's model for the healthy subjects was properly justified.

### **Population PK analysis of the combined data sets for healthy subjects and pediatric patients**

In the final data analysis, the applicant included 739 gabapentin plasma concentration data from 253 subjects. Gabapentin plasma concentrations for the patients were measured in the wider range (standard curves up to 20 mcg/mL) than for the healthy subjects (standard curves up to 7 mcg/mL). The limit of quantitation for the safety and efficacy studies ranged between \_\_\_\_\_ The doses ranged from 10 to 66 mg/kg/day, and the time of post-dose collection ranged from 0.08 to 21.3 hrs. From these data collections, the healthy subjects' data were obtained on the first day and the patients' data were obtained (at steady state, TID) on days 2-4.

The applicant repeated the steps for the initial model building for the healthy subjects with the combined data set. Although the variability in the combined data set was larger, the model built for the healthy subjects was accepted for this population as well.

Then the applicant identified the basic structural model by incorporating covariates one at a time in the model and evaluating if this will explain inter-subject variability in the pharmacokinetic parameters. Table 9 (Appendix A) summarizes the effects of covariates on the parameters. The most important covariates were race, formulation, use of phenytoin on CL/F, and study population on V/F. These covariates were reevaluated (Table 10, Appendix A).

The applicant then removed each of the important covariates from the model by fixing the coefficient to zero. At this step proper adjustment of p value for the multiple comparison was performed.

The FDA re-ran the final model for the combined population data. The applicant did not include all parameters in the POSTHOC section for the evaluation of goodness of fit. Therefore, FDA added in the POSTHOC section all ETAs, WRES, PRED. The obtained output was very similar to the applicant's one. The parameters calculated with POSTHOC option were used for the graphic model diagnostics.

All plots presented by the applicant were the same when created by the FDA.

The FDA attempted to use METHOD 1 in the ESTIMATION record of NONMEM. This led to the statistically significant (19 units) decrease in the objective function; however, the program failed to obtain a desirable accuracy of parameter estimates and the covariance step was aborted. Therefore, METHOD 0 was accepted as an estimation method for the final model.

Although the plot of WRES vs. PRED (Figure 4) shows the trend for the patient population (light color of circles), the data of combined population were equally spread around of the zero values.

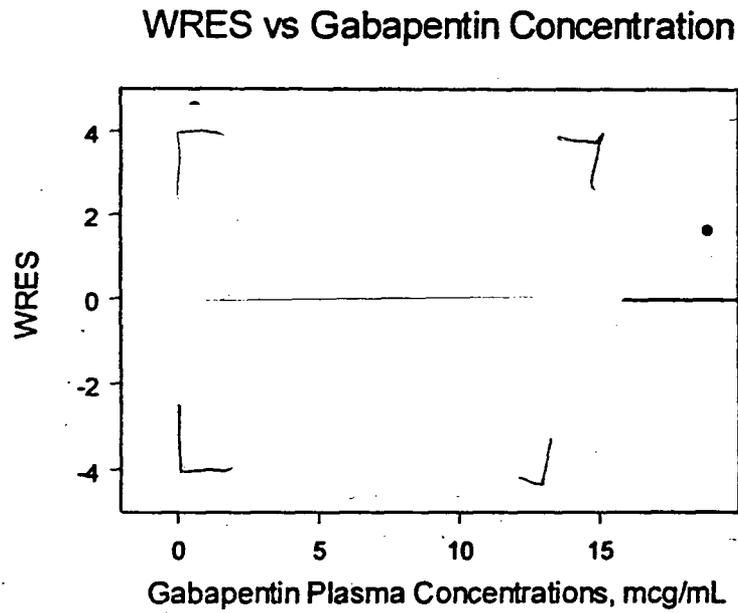


Figure 4. WRES vs. gabapentin plasma concentrations. Light color circles are for the patient's data, dark color circles are for the healthy subject's data.

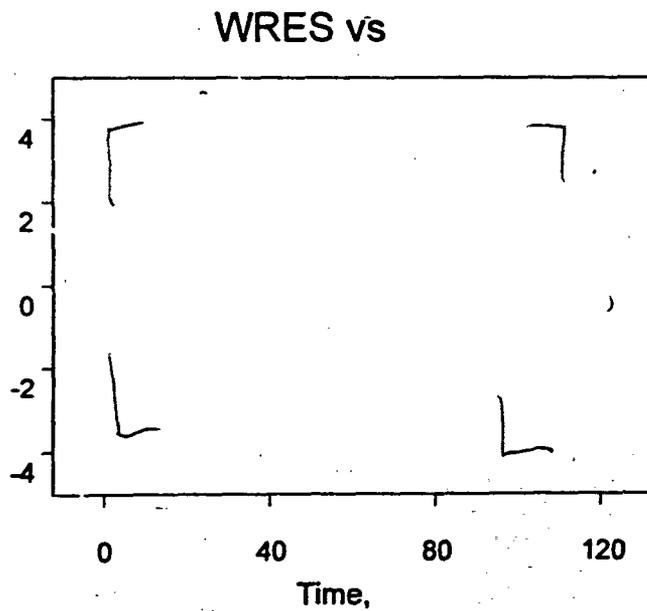


Figure 5. WRES vs. time. Large circles are for the patient's data, small circles are for the healthy subject's data.

The plot of WRES vs. time (Figure 5 above) indicates an equal distribution of WRES around the zero values.

FDA plotted the parameter estimates (CL, V, ka, tlag) vs. ETAs. The matrix plot demonstrates that there are no trends in the relationships between the parameters and ETAs, as shown in Figure 6 below.

## PK Parameters vs ETAs

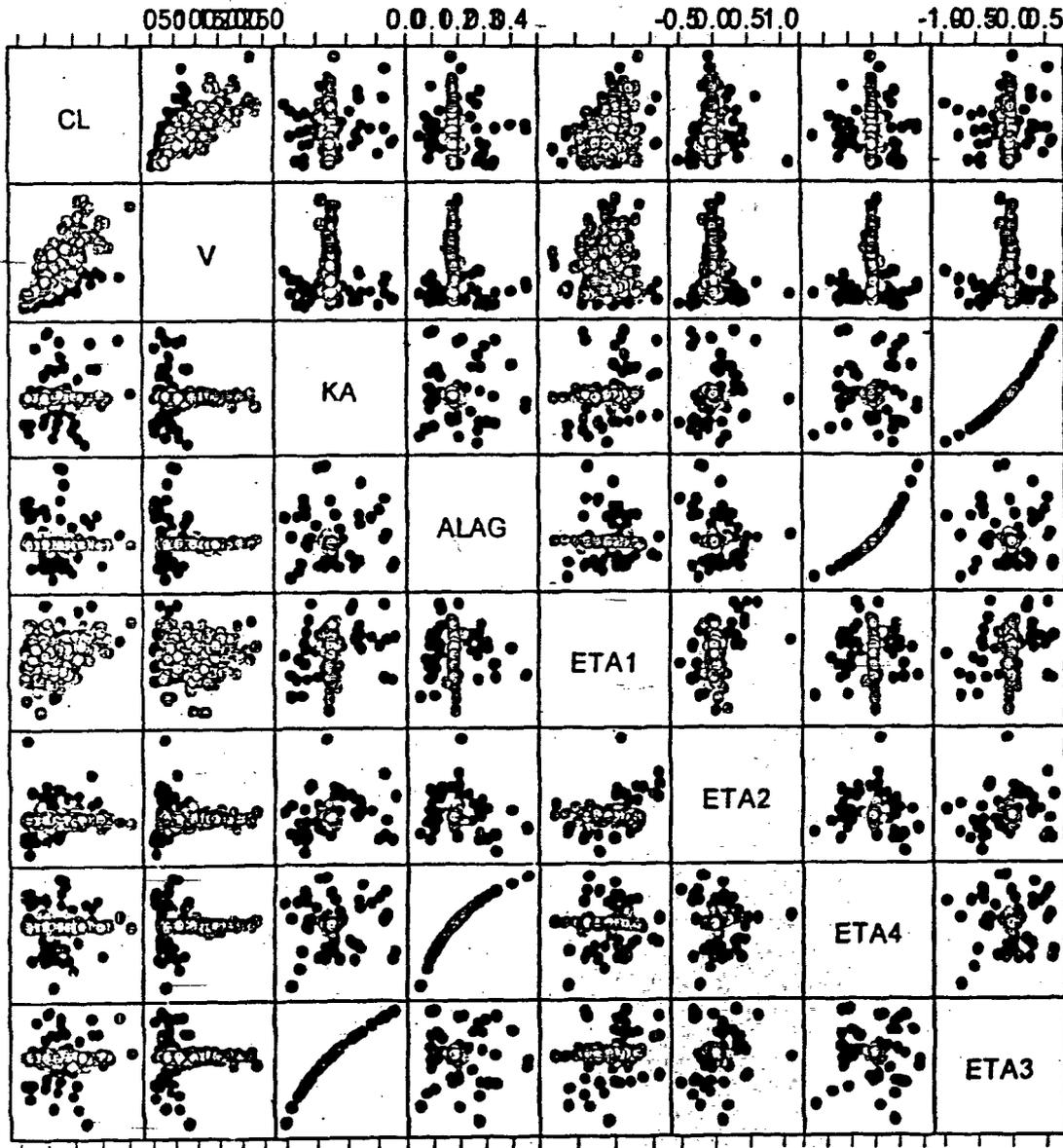


Figure 6. PK parameters for healthy subjects and patients vs. covariates. . Lighter circles are for the patient's data, darker circles are for the healthy subject's data.

The plot of pharmacokinetic parameters vs. covariates (age, race, body weight, and creatinine clearance) is shown in Figure 7. Clearance and creatinine clearance were strongly correlated, which is reasonable due to the renal excretion of gabapentin.

## PK Parameters vs Covariates

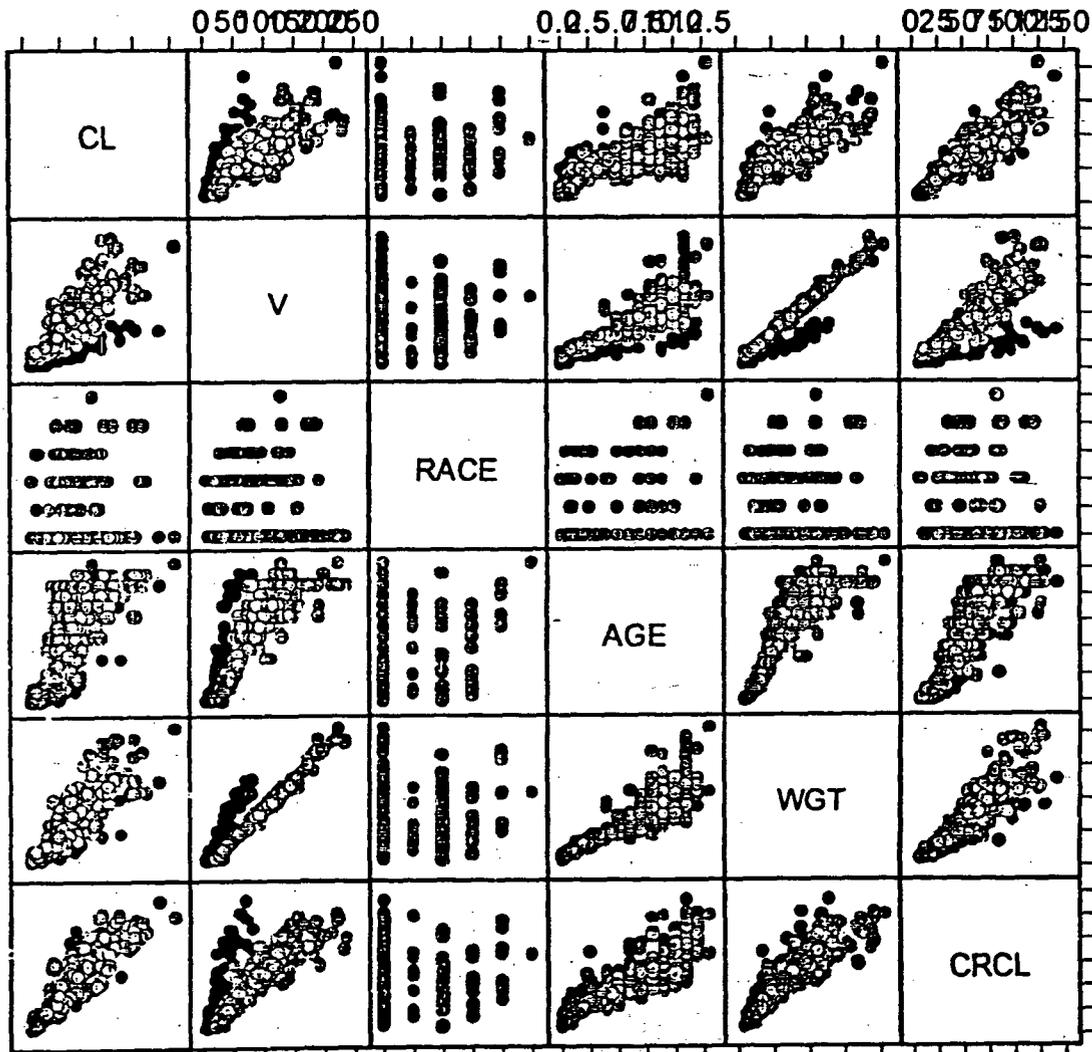


Figure 7. PK parameters vs. covariates. Lighter circles are for the patient's data, darker circles are for the healthy subject's data.

The matrix plot of normalized by body weight clearance and volume of distribution vs. covariates (age, race, body weight, and creatinine clearance) is shown in Figure 8.

## PK Parameters vs Covariates

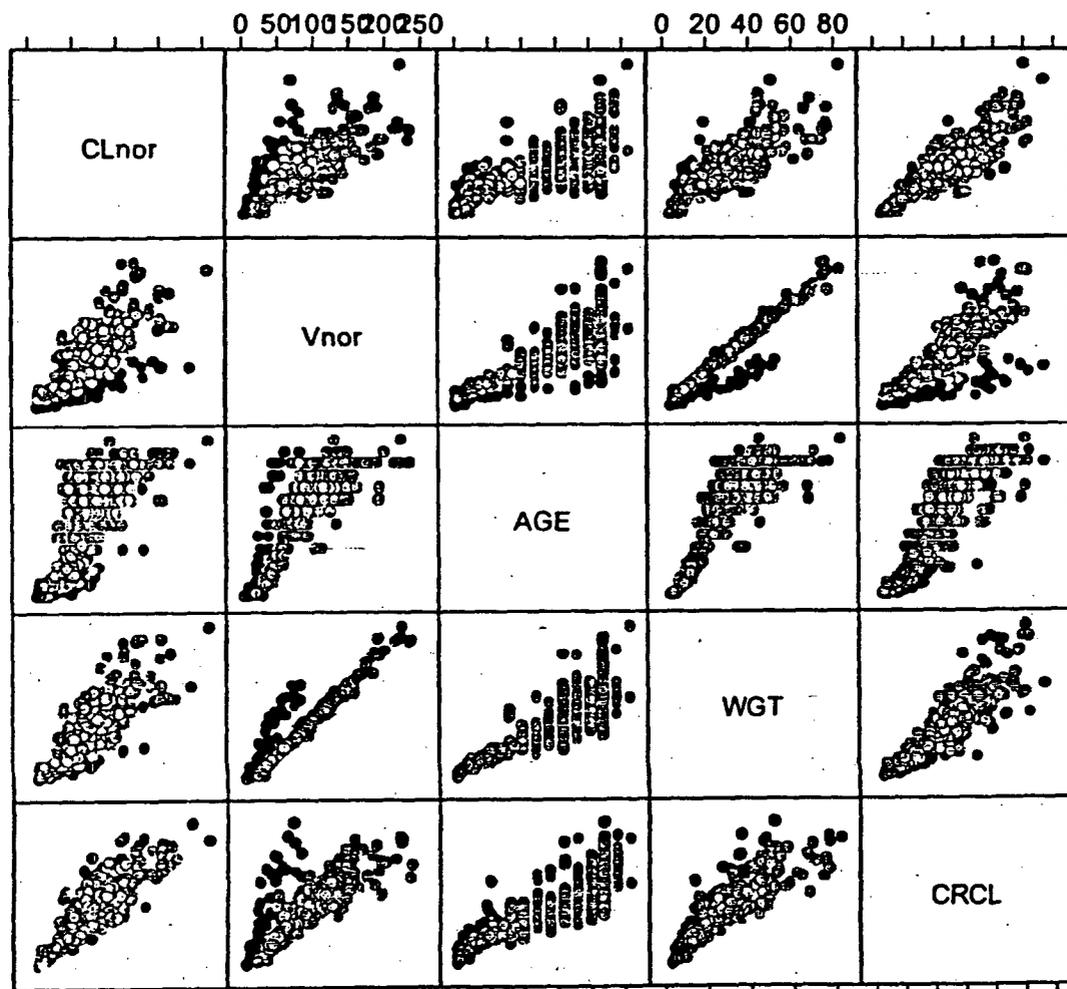


Figure 8. Clearance and volume of distribution normalized by body weight vs. covariates. Lighter circles are for the patient's data, darker circles are for the healthy subject's data

Clearance values normalized by body weight in small children (under 5 years old) were higher and more variable than in other age group (Figure 9). On average, the post-hoc estimates of normalized CL/F were 30% larger for the children younger than 5 years old. This finding is the basis for the 30% of dose adjustment proposed for in this group of children. Additionally, non-compartmental data analysis of all subjects indicates that the increase of the dose in small children by 50% is necessary to achieve the same exposure as in the age group of 5-12 years old.

FDA compared the clearance normalized by body weight values for the groups of children  $\leq 5$  and  $>5$  and 12 years old. T-test showed that younger children had statistically significant increase in clearance values, as shown below.

Table. T-test for Comparison of groups of children of 0-5 and 5-12 years old

t-Test: Two-Sample Assuming Unequal Variances		
	0-5 years old children	5-12 years old children
Mean	0.355920729	0.28884029
Variance	0.021698012	0.01511247
Observations	329	410
Hypothesized	0	
Mean Difference		
df	637	
t Stat	6.615702436	
P(T<=t) one-tail	3.92186E-11	
t Critical one-tail	1.647249519	
P(T<=t) two-tail	7.84371E-11	
t Critical two-tail	1.963694558	

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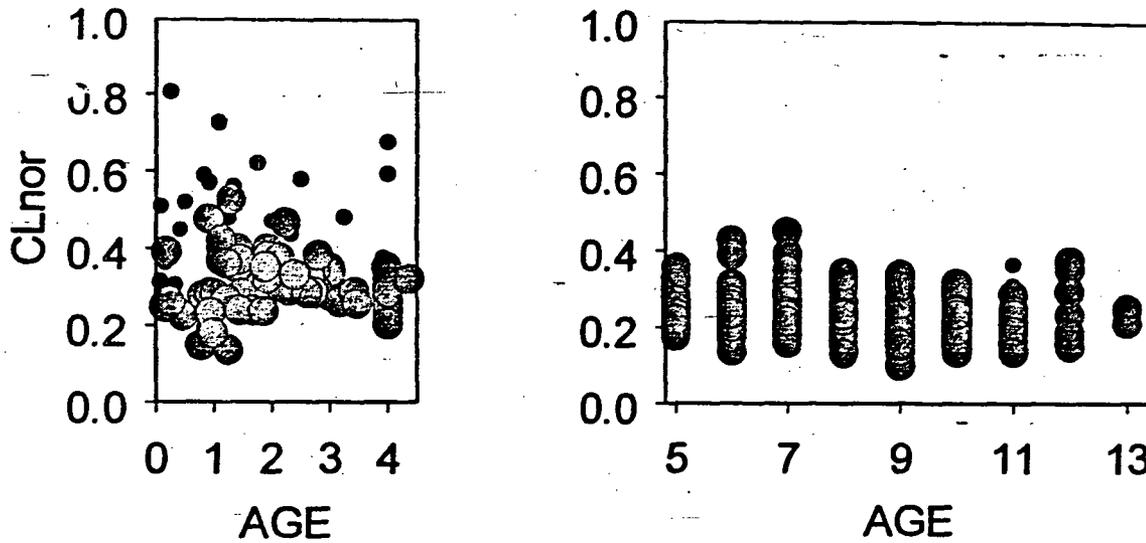


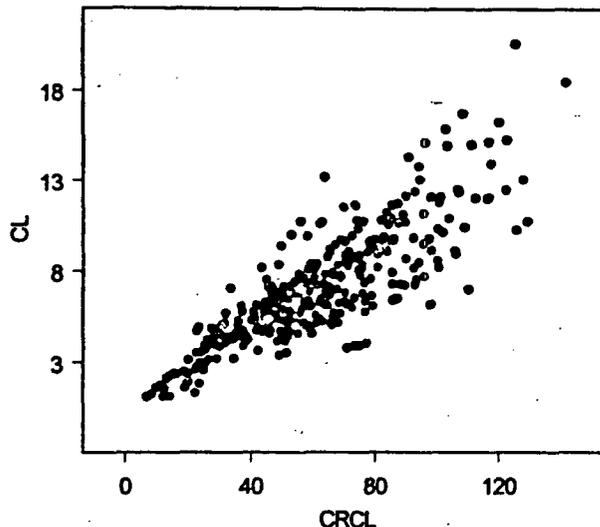
Figure 9. Clearance normalized by body weight vs. age. Light color of circles are for the patients, dark color of circles are for the healthy subjects.

Therefore, children less than 5 years old were recommended to have dose adjustment from 30 to 40 mg/kg/day. This dose adjustment is properly included in the Package Insert.

It appeared that the CL and volume of distribution depend on the population (healthy subjects and patients). However, the NONMEM run performed by the FDA without accounting for the population shows that this difference was not pronounced.

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### Clearance vs CLcr for Black vs All Other Subjects



*Figure 11. Clearance vs. creatinine clearance. Light color of circles are for the blacks, dark color of circles are for the other subjects*

All the graphic diagnostics together with the re-run of the model confirms the finding by the applicant.

#### Comments:

1. The applicant omitted about 46% of the originally reported data due to improper data records (unreported time of last dose, unreported time of the plasma samples, absence of demographic data). Based on the data, which were appropriately collected for the pharmacokinetic analysis, the applicant adequately performed the population analysis of the combined pediatric data from 7 studies: two studies with the rich data from healthy subjects and 5 studies with sparse sampling data obtained from the patients. Overall, the estimation of pharmacokinetic parameter values seems reasonable. This data analysis adds value to the corrections of the Package Insert.
2. Gabapentin oral clearance was directly related to creatinine clearance, which was expected because gabapentin is exclusively eliminated by the kidney. This was supported by the estimate of zero obtained for the intercept of this relationship.

3. Gabapentin clearance normalized by body weight was on average 30% larger in the group of children 5 years and younger. In the Package Insert, the dose for the children younger than 5 years old was adequately adjusted to 40 mg/kg/day.
4. Clearance was estimated to be 36% higher in black subjects in comparison with all other races. Although this increase of clearance seems to be high, the applicant properly concluded that it is not clinically significant because the posthoc estimated clearance values for black subjects were in the range of clearance values for all subjects.
5. Gabapentin volume of distribution directly correlated with body weight, and intercept of this relationship was proved to be zero. Volume of distribution normalized by the body weight showed bimodal distribution for the healthy subjects and for the patients. Larger gabapentin volume of distribution observed for the patients was not fully explained by the applicant. The most important reason listed in the report probably is the statistical difference between the two data sets (intense sampling scheme vs. sparse sampling) which could lead to the biases in the parameter estimations.
6. Population data analysis showed that the influence of body surface area, gender, height, formulation, disease (population), co-administration of phenytoin, phenobarbital, valproic acid, carbamazepine, vigabatrin on clearance was statistically insignificant. The covariates did not affect the estimation of the rate of gabapentin absorption and the lag-time values.
7. Population data analysis showed that the influence of age, gender, race, formulation on volume of distribution of gabapentin was statistically insignificant. The covariates did not affect the estimation of the rate of gabapentin absorption and the lag-time values.
8. In the final model for the combined data set, inter-subject variability was about 30% for both CL/F and V/F, 43% for  $k_a$  and 79% for  $t_{lag}$ . In healthy subjects, the residual variability (proportional: CV=10%, additive: 0.25 mcg/mL) was much smaller than the same for the pediatric patients (proportional: CV=25%, additive: 1.32 mcg/mL). This difference in variability was explained by the difference in the assay concentration ranges for these populations.
9. The applicant did not perform a proper model validation by splitting the full data set for index and validation sets.
10. The applicant did not consider the inter-occasion variability for the patients data obtained at steady state. Although the number patients studied on different occasions was small, incorporation of inter-occasion variability may account for the unexplained variabilities on parameter estimates.



**APPENDIX A**  
**Applicant's Data**

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Table 1. Study Design Summary  
(Page 1 of 2)

Protocol	Design	Duration	Population	Sampling	Dose	Formulation
-202	Open-label	Single Dose	Healthy subjects aged 4-12 years	Day 1 at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 14, and 24 hr postdose	~10 mg/kg as 200, 300, or 400 mg per dose	—
-296	Open-label	Single Dose	Healthy subjects aged 1 month to 4 years	Day 1 at 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 hr postdose	10 mg/kg	Syrup 50 mg/mL
-86/186	Double-blind, parallel, placebo-controlled, randomized	18 weeks (6 week-baseline and 12 week-treatment)	Patients able to swallow tablets (age 3) up to 12 years with refractory partial seizures	Visit 2 (Week 10) and Visit 4 (Week 18)	Daily dose of 24-35 mg/kg in 3 doses at 8:00, 14:00, and 20:00 as 200, 300, 400, and 600 mg per dose	Size 2 capsules of 100 and 200 mg.
-94	Double-blind, parallel, placebo-controlled, randomized	36 weeks	Patients aged 4-13 years with benign childhood epilepsy with centrotemporal spikes (BECTS)	Visit DB2 (Week 2), DB6 (Week 16), and DB9 (Week 36)	Daily dose of ~30 mg/kg in 3 doses at 8:00, 14:00, and 20:00 as 200, 300, 400, and 600 mg per dose	Size 2 capsules of 100 and 200 mg.
-95	Open-label (extension of Study -94)	96 weeks	Same subjects as Study -94 above	Visits 2, 6, 7, 8, 9, 10, and Behavioral/Cognitive (B/C) Visit (6 months after the second B/C Visit of -94). the protocol was modified to B/C Visit only.	Daily dose of 15-60 mg/kg in 3 doses at 8:00, 14:00, and 20:00	Capsules of 100, 200, 300, and 400 mg.

AED = Antiepileptic drugs.

Table 1. Study Design Summary  
(Page 2 of 2)

Protocol	Design	Duration	Population	Sampling	Dose	Formulation
-305/405	Double-blind, parallel, placebo-controlled, randomized	Minimum 2 day-Baseline and 3 day-Treatment	Patients aged 1 month to 3 years with partial seizures not adequately controlled by at least one current AED	DB4/Termination (Day 4 Treatment period)	Daily dose of ~40 mg/kg in 3 doses at 8:00, 14:00, and 20:00	Syrup 50 mg/mL
-301/401	Open-Label (extension of 305/405 study and <i>de novo</i> patients)	52 weeks	Patients aged 1 month through 4 years with seizures uncontrolled by current AED	V3 (2 months) and V5 (6 months)	Daily dose of 40-60 mg/kg in 3 doses at 8:00, 14:00, and 20:00	Syrup 50 mg/mL

AED = Antiepileptic drugs.

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Table 2. Variables Included in the NONMEM Data Set

Variable	Definition	Categories/Units
ID	Subject Identification Number created as a composite of Protocol Number, Subject Number and Site Number	
NMID	NONMEM Identification Number	
PROT	Protocol Number	94, 95, 186, 202, 296, 301, 305, and 405
FORM	Formulation Administered	1 = Capsule; 0 = Syrup
DOSE	Dose Administered	mg
DOS2	Dose Administered per kg	mg/kg
AMT1	Amount (Dose) for Dosing Event	mg
AMT2	Amount per kg (Dose) for Dosing Event	mg/kg
TIME	Relative Time	hours
DV	Dependent Variable (Gabapentin concentration)	µg/mL
MDV	Missing Data Value	0 = observation; 1 = other
EVID	Event Identification Data Item	0 = observation; 1 = dose; 4 = reset dose
SS	Steady-State Data Item	0 = not steady-state dose; 1 = reset steady-state dose; or 2 = steady-state dose
II	Interdose Interval Data Item	hr
VIS	Visit Number	Value depends on Specific Study; B/C visit in Study -95 coded as 20
AGE	Age	years
HT	Height	cm
WGT	Weight	kg
BSA	Body Surface Area	m <sup>2</sup>
GDR	Gender	1 = male; 0 = female
RACE	Race	1 = Caucasian; 2 = Black; 3 = Hispanic; 4 = Asian; 5 = Native Indian; 6 = Other
nCRC	Creatinine Clearance Normalized per 1.73 m <sup>2</sup>	mL/min/1.73 m <sup>2</sup>
CrCL	Creatinine Clearance	mL/min
PRM	Primidone	1 = Yes; 0 = No
ETH	Ethosuximide	1 = Yes; 0 = No
VPA	Valproic Acid	1 = Yes; 0 = No
PB	Phenobarbital	1 = Yes; 0 = No
CBZ	Carbamazepine	1 = Yes; 0 = No
LTG	Lamotrigine	1 = Yes; 0 = No
CLB	Clobazam	1 = Yes; 0 = No
CLM	Clonazepam	1 = Yes; 0 = No
OCZ	Oxcarbazepine	1 = Yes; 0 = No
VGB	Vigabatrin	1 = Yes; 0 = No

**Table 3. Dosing Information, Gabapentin Concentrations, and Time of Collection (Mean ± SD; Range)**

Study	N conc	Dose (mg/kg)		Concentration (µg/mL)		Time postdose (hr)	
202	240 <sup>a</sup>	9.33 ± 1.09	(7.68-12.2)	2.33 ± 1.64	(0.05-6.94)	0.5, 1, 2, 3, 4, 6, 8, 10, 14, 24	
296	182 <sup>a,b</sup>	10.0 ± 0.0	(NA)	1.84 ± 1.35	(0.04-7.00)	0.5, 1, 2, 4, 6, 8, 12, 24	
94	89	9.29 ± 1.67	(3.32-15.7)	5.39 ± 2.37	(0.50-10.1)	4.50 ± 3.52	(0.25-17.6)
95	67	11.30 ± 3.60	(4.58-21.1)	5.65 ± 3.15	(0.50-16.2)	5.27 ± 3.40	(0.58-21.3)
86/186	104 <sup>c</sup>	9.63 ± 1.89	(4.94-21.9)	4.52 ± 2.41	(0.76-10.5)	6.25 ± 4.91	(0.08-14.7)
305/405	30	13.41 ± 0.88	(11.5-15.4)	3.39 ± 1.87	(0.23-8.05)	6.06 ± 4.47	(0.50-12.5)
301/401	27 <sup>d</sup>	15.2 ± 2.67	(9.38-21.7)	6.50 ± 3.25	(0.81-18.9)	3.93 ± 1.61	(1.67-7.53)

NA = Not applicable.

<sup>a</sup> This number excludes all predose concentrations reported as 0 µg/mL.

<sup>b</sup> This number excludes 10 gabapentin concentrations reported as 0 µg/mL 24 hours postdose.

<sup>c</sup> This number excludes 5 gabapentin concentrations reported as 0 µg/mL in 4 patients.

<sup>d</sup> This number excludes 1 gabapentin concentration reported as 0 µg/mL.

**Table 4. Characteristics of the Pediatric Population: Continuous Variables<sup>a</sup> (Mean ± SD)**

Study	N	Age (yr)	Weight (kg)	Height (cm)	BSA (m <sup>2</sup> )	CrCL (mL/min)
202	24	8.7 ± 2.8	33.8 ± 10.6	134 ± 15	1.11 ± 0.23	91.8 ± 23.5
296	24	1.3 ± 1.1	9.5 ± 3.6	75 ± 15	0.43 ± 0.13	33.9 ± 17.2
94/95	96	8.1 ± 2.1	35.2 ± 14.1	134 ± 16	1.13 ± 0.27	65.3 ± 20.1
86/186	66	8.1 ± 2.4	31.8 ± 11.7	132 ± 16	1.07 ± 0.25	69.2 ± 21.2
301/401/305/405	43	1.9 ± 1.0	12.0 ± 3.4	84 ± 12	0.51 ± 0.11	28.2 ± 11.1
All Studies	253	6.5 ± 3.6	27.8 ± 15.1	119 ± 28	0.94 ± 0.36	59.3 ± 27.1
(Range)		(0.08-13)	(3.6-82.9)	(51-178)	(0.21-1.95)	(7.1-142)

<sup>a</sup> Value of the variable at the time of screening.

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Table 9. Summary of the Effect of Individual Covariates on Pharmacokinetic Parameters

Covariate Model	MOF	ΔMOF	Rank
1. Basic model (Model 8, Table 8)	502.533	--	--
2. $CL/F = \theta_1 + \theta_{CrCL} \cdot CrCL + \theta_{AGE} \cdot AGE$	496.729	-5.804	--
3. $CL/F = \theta_1 + \theta_{CrCL} \cdot CrCL + \theta_{WGT} \cdot WGT$	502.204	-0.329	--
4. $CL/F = \theta_1 + \theta_{CrCL} \cdot CrCL + \theta_{HT} \cdot HT$	501.612	-0.921	--
5. $CL/F = \theta_1 + \theta_{CrCL} \cdot CrCL + \theta_{BSA} \cdot BSA$	501.814	-0.719	--
6. $CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{GDR} \cdot GDR)$	501.736	-0.797	--
7. $CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{RAC} \cdot RAC)$	489.292	-13.241	2
8. $CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{POP} \cdot POP)$	Rounding Error		--
9. $CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{FORM} \cdot FORM)$	495.153	-7.38	5
10. $CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{PHT} \cdot PHT)$	490.981	-11.552	3
11. $CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{VPA} \cdot VPA)$	502.190	-0.343	--
12. $CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{PB} \cdot PB)$	498.868	-3.665	--
13. $CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{CBZ} \cdot CBZ)$	500.307	-2.226	--
14. $CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{VGB} \cdot VGB)$	498.307	-4.226	--
15. $Vd/F = \theta_2 + \theta_{WGT} \cdot WGT + \theta_{AGE} \cdot AGE$	502.529	-0.004	--
16. $Vd/F = (\theta_2 + \theta_{WGT} \cdot WGT) \cdot (1 - \theta_{GDR} \cdot GDR)$	502.187	-0.346	--
17. $Vd/F = (\theta_2 + \theta_{WGT} \cdot WGT) \cdot (1 - \theta_{RACE} \cdot RACE)$	Rounding Error		--
18. $Vd/F = (\theta_2 + \theta_{WGT} \cdot WGT) \cdot (1 - \theta_{POP} \cdot POP)$	461.856	-40.677	1
19. $Vd/F = (\theta_2 + \theta_{WGT} \cdot WGT) \cdot (1 - \theta_{FORM} \cdot FORM)$	501.449	-1.084	--
20. $ka = \theta_3 + \theta_{AGE} \cdot AGE$	500.307	-2.226	--
21. $ka = \theta_3 \cdot (1 - \theta_{POP} \cdot POP)$	492.716	-9.817	4
22. $ka = \theta_3 \cdot (1 - \theta_{FORM} \cdot FORM)$	502.173	-0.360	--
23. $t_{lag} = \theta_4 + \theta_{AGE} \cdot AGE$	500.422	-2.111	--
24. $t_{lag} = \theta_4 \cdot (1 - \theta_{POP} \cdot POP)$	502.028	-0.505	--
25. $t_{lag} = \theta_4 \cdot (1 - \theta_{FORM} \cdot FORM)$	498.676	-3.857	--

Table 10. Summary of Covariate Model Building Steps in All Pediatric Subjects

Model	Description (Reference Model)	MOF	ΔMOF	Significant?
1	Model 8 (Table 8)	502.533	--	--
2	$Vd/F = (\theta_2 + \theta_{WGT} \cdot WGT) \cdot (1 - \theta_{POP} \cdot POP)$ on (1)	461.856	-40.677	YES
3	$CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{RAC} \cdot RAC)$ on (2)	449.637	-12.219	YES
4	$CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{RAC} \cdot RAC) \cdot (1 - \theta_{PHT} \cdot PHT)$ on (3)	444.457	-5.18	NO
5	$ka = \theta_3 \cdot (1 - \theta_{POP} \cdot POP)$ on (3)	448.963	-0.674	NO
6	$CL/F = (\theta_1 + \theta_{CrCL} \cdot CrCL) \cdot (1 - \theta_{RAC} \cdot RAC) \cdot (1 - \theta_{FORM} \cdot FORM)$ on (3)	442.959	-6.959	YES

MOF = Minimum Objective Function.  
 ΔMOF = Change in MOF.

Thus, in the final pharmacokinetic model in healthy pediatric subjects, gabapentin oral clearance was directly related to creatinine clearance. This was expected since gabapentin is exclusively eliminated via the kidneys. The apparent volume of distribution was related to body weight. This result was expected as well since the dose used to perform the analysis was not normalized per body weight. This indicates that when Vd/F is normalized per body weight, it is constant across the different weight range. The final population pharmacokinetic parameter estimates are summarized in Table 7. Residual variability was described with a proportional coefficient of variability of 9.39% and a standard deviation for the additive error term of 0.105 µg/mL. The NONMEM output is provided in Appendix D.

Table 7. Population Pharmacokinetic Parameter Estimates in Healthy Subjects

Pharmacokinetic Parameter	$\theta$ (95% CI)	%CV (95% CI)
$CL/F = \theta_{CrCL} \cdot CrCL$ (L/h)	0.130 (0.116-0.144)	38.3 (24.2-48.5)
$Vd/F = \theta_{WGT} \cdot WGT$ (L)	1.62 (1.47-1.77)	31.6 (23.1-38.3)
$k_a$ (hr <sup>-1</sup> )	1.26 (1.03-1.49)	45.5 (32.1-55.8)
$t_{lag}$ (hr)	0.184 (0.103-0.265)	82.5 (0-123)

#### 5.4. Pharmacokinetics in Healthy Pediatric Subjects and Pediatric Patients

Plasma concentration-time data (n = 739 concentrations) from all subjects (n = 253) were combined and included in this final analysis. Concentration-time data from the pediatric patients are illustrated in Figure 3 (refer to Figure 2 for the pharmacokinetic profile in healthy pediatric subjects). Gabapentin concentrations ranged from 0.23 to 18.9 µg/mL including all doses which ranged from 3.3 to 21.9 mg/kg corresponding to total daily doses ranging from 10 to 66 mg/kg/day. The time of sample collection varied between 0.08 to 21.3 hours with an average time of collection of approximately 5 hours postdose.

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## Global Research & Development

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To: Jackie Ware, PharmD Date: September 1, 2000

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Location: FDA, DNDP

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Telephone: 301-594-5533 Fax: 301-594-2859

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From: Robin Pitts, R.Ph.

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Extension: 734 622-x5628 Fax: 734 622-3283

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Normal  Urgent  Confidential

Re: Minutes of Teleconference to Discuss NDA: 21-216 Neurontin (gabapentin) pediatric supplement

Reference is made to our August 31, 2000 teleconference between Dr. Maria Sunzel of the Division of Pharmaceutical Evaluation I and Dr. Howard Bockbrader and myself of Pfizer to discuss the population-PK analysis for the gabapentin pediatric clinical trials. During that conversation she expressed concern that the population-PK analysis only included 54% of the plasma samples drawn in the gabapentin pediatric clinical trials. She requested that we contact Dr. Elena Mishina of DPE1 to further discuss the analysis.

On August 31, 2000, Dr. Bockbrader and I contacted Dr. Mishina to discuss the population-PK analysis. We informed her that the 46% of samples not included in the population analysis were mainly from Studies 945-86/186 and 945-95. In Studies 945-86/186, the samples were collected for compliance and not collected for PK purposes. The times when the last dose was administered and time of the blood sample were not collected. This information is necessary for the assumptions used in the model used in the population analysis. In Study 945-95, the 1 year

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NDA 21-216: Neurontin® (gabapentin oral solution)  
NDA 20-235/S-015: Neurontin® capsules; NDA 20-882/S-002: Neurontin® tablets

SEP 01 2000 10:45 AM MARK-DRAVIS FDA LIAIS734 622 3283 TO 913015942859 P.02/02  
To: Jackie Ware, PharmD  
September 1, 2000  
Page 2

open label extension, samples were not included in the analysis that had missing demographic information. Since this study was performed in children and the children were enrolled for 1 year, it was felt that using the demographic information from a previous visit may not be indicative of growth changes in the children.

If you have any questions or comments, please feel free to contact Jan Turner at 734-622-7426 or myself at 734-622-5628. We will also submit a copy of this fax to the NDA.

Regards,

  
Robin Pitts

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