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Pregabalin has shown clinical efficacy for treatment of neuropathic pain syndromes, partial seizures, and anxiety disorders. Five studies in healthy volunteers are performed to investigate single- and multiple-dose pharmacokinetics of pregabalin. Pregabalin is rapidly absorbed following oral administration, with peak plasma concentrations occurring between 0.7 and 1.3 hours. Pregabalin oral bioavailability is approximately 90% and is independent of dose and frequency of administration. Food reduces the rate of pregabalin absorption, resulting in lower and delayed maximum plasma concentrations, yet the extent of drug absorption is unaffected, suggesting that pregabalin may be administered without regard to meals. Pregabalin elimination half-life is approximately 6 hours and steady state is achieved within 1 to 2 days of repeated administration. Corrected for oral bioavailability, pregabalin plasma clearance is essentially equivalent to renal clearance, indicating that pregabalin undergoes negligible nonrenal elimination. Pregabalin demonstrates desirable, predictable pharmacokinetic properties that suggest ease of use. Because pregabalin is eliminated renally, renal function affects its pharmacokinetics.

Keywords: *Pregabalin; clinical pharmacokinetics; neuropathic pain; epilepsy*

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Pregabalin [CI-1008; isobutyl γ-aminobutyric acid; (*S*)-(+)-3-(aminomethyl)-5-methylhexanoic acid] is an $\alpha_2\delta$ ligand that has analgesic, anxiolytic, and anticonvulsant activity. $\alpha_2\delta$ is an auxiliary protein subunit associated with voltage-gated calcium channels. Pregabalin binds potently to this $\alpha_2\delta$ subunit[1] and reduces calcium influx at nerve terminals. This, in turn, limits the release of several neurotransmitters, including glutamate, noradrenaline, and substance P.[2-5] These properties result in pregabalin showing activity in a variety of preclinical models of pain,[6-13] seizures,[14-16] and anxiety.[17] Pregabalin has been investigated in clinical trials and has been found efficacious and safe as treatment for neuropathic pain syndromes, including painful diabetic peripheral neuropathy[18-21] and postherpetic neuralgia,[18,22,23] with both doses titrated from 150 mg/d over the course of 1 week to a maximum recommended dose of 300 mg/d (with creatinine clearance at least 60 mL/min). Pregabalin has also been approved for add-on treatment of partial seizures[24-29] (titrated from 150 mg/d [75 mg twice a day or 50 mg 3 times a day] over 1 week or as tolerability allows to maximum recommended dose of 600 mg/d), for the treatment of anxiety disorders,[28,30-33] and for fibromyalgia syndrome[26] (both doses titrated from 150 mg/d over the course of 1 week based on efficacy and tolerability to a maximum recommended dose of 300-450 mg/d with creatinine clearance at least 60 mL/min).

As part of the clinical development of pregabalin, single- and multiple-dose pharmacokinetics were characterized in healthy volunteers in 3 studies. The effect of food on pregabalin pharmacokinetics was assessed in 2 additional studies. Results of these studies are summarized herein to provide a pharmacokinetic profile of pregabalin.

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SUBJECTS AND METHODS

Subjects

In total, 112 healthy subjects received pregabalin in 5 studies designed to characterize pregabalin pharmacokinetics. Subject characteristics are summarized in Table I. All subjects were in good health, as determined by medical history, physical examination, electrocardiography, Holter monitoring (only performed in the 3 single- and multiple-dose pharmacokinetics studies), and clinical laboratory measurements. All studies were carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and all subjects provided written informed consent before entering a study. Protocols were approved by the Institutional Review Boards at the sites where the studies were conducted: PPD, Inc., Austin, Texas; Corning Besselaar Clinical Research Units, Madison, Wisconsin; and Community Research Clinic, Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan.

Single- and Multiple-Dose Pharmacokinetics (Studies 1-3)

Single-dose pharmacokinetics were assessed in a randomized, double-blind, 2-way crossover, rising-dose study (study 1). On 2 occasions, 1 week apart, groups of 6 subjects received either placebo (n = 3) or 1 dose of pregabalin (n = 3). Pregabalin was dosed at 1 and 2 mg (group 1, weeks 1 and 2), 5 and 10 mg (group 2, weeks 4 and 5), 25 and 50 mg (group 3, weeks 7 and 8), 75 and 125 mg (group 4, weeks 10 and 11), and 200 and 300 mg (group 5, weeks 13 and 14). Dose escalations were based on absence of significant adverse events and maintenance of systemic pregabalin exposure below a preset limit. The 1- and 2-mg doses were administered in solution; all other doses were administered as capsules. Venous blood samples were collected before each dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 60 hours after the dose. Subjects were instructed to empty their bladders immediately before each dose, and a 100-mL urine sample was retained. Thereafter, all urine voided during the time intervals of 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 60 hours postdose was collected and the volume recorded.

Both single- and multiple-dose pregabalin pharmacokinetics were characterized in 2 studies. The first was a randomized, double-blind, placebo-controlled, parallel-group, staggered-start, rising-dose study (study 2) in which subjects were dosed for 2 weeks according to the schedule given in Table II. In an additional randomized, double-blind, placebo-controlled study (study 3), 12 subjects were dosed with pregabalin 300 mg every 8 hours for 28 days, with a single 300-mg dose administered on day 29, while 3 subjects received placebo every 8 hours for 28 days, with a single dose of placebo on day 29. All doses were administered as capsules in these 2 studies.

In study 2 (2 weeks), venous blood samples were collected before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 60 hours after the dose on days 1 and 22. In addition, blood samples were drawn prior to the morning dose on days 8, 9, 10, 12, 15, and 18. Subjects were instructed to empty their bladders immediately before the dose on days 1 and 22, and a 100-mL urine sample was retained from each collection. All urine voided during the time intervals of 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 60 hours after dosing on days 1 and 22 was collected and the volume recorded.

In the 4-week study (study 3), blood samples were collected before and 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours following the morning dose on day 1. Blood samples also were collected before the morning dose on days 2, 3, 4, 7, 11, 14, 18, 22, and 26 and before and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours following the morning dose on day 29.

On pharmacokinetic sampling days in all 3 studies, subjects were required to fast overnight for at least 8 hours. On days when full pharmacokinetic profiles were obtained, subjects remained fasting for 4 hours following the morning dose. Identical lunches and dinners were served on these days. On other days during multiple dosing, doses were administered either 2 hours before or 2 hours after a meal. Each dose was administered with 8 oz of water, and capsules were swallowed intact.

Effect of Food on the Pharmacokinetics of Pregabalin (Studies 4-5)

The effect of food on pregabalin pharmacokinetics was assessed in 2 studies. The first (study 4) was an open-label, single-dose, randomized, 3-way crossover study in which the effect of a standard breakfast was assessed and bioavailability of capsules relative to solution was evaluated. On 3 occasions, 10 days apart, 12 subjects received the following treatments in random order: (1) one 100-mg pregabalin capsule after an overnight fast; (2) 100 mg of pregabalin in solution after an overnight fast; and (3) one 100-mg pregabalin capsule 15 minutes after beginning to eat a 1000-kcal standard breakfast. Subjects were randomized to 1 of

Table I Summary of Subject Characteristics

Study	Description	Dose	No. on Active Treatment	Mean Age, y (Range)	Mean Weight, kg (Range)	Gender
1	Single-dose pharmacokinetics	1, 2, 5, 10, 25, 50, 75, 125, 200, or 300 mg	29	40.1 (29-49)	77.4 (60.2-91.1)	14 men, 15 women
2	Single- and multiple-dose pharmacokinetics (2 weeks)	25, 100, 200, 300 mg every 8 h or 300 mg every 12 h	45	35.3 (19-50)	75.5 (60.6-93.5)	29 men, 16 women
3	Single- and multiple-dose pharmacokinetics (4 weeks)	300 mg every 8 h	12	31.8 (19-48)	75.0 (60.8-85.1)	11 men, 1 woman
4	Effect of food on pharmacokinetics	100 mg every 24 h days 1, 11, 21	12	54.1 (38-64)	69.8 (55.5-91.5)	1 man, 11 women
5	Effect of food on pharmacokinetics	150 mg every 24 h days 1, 8	14	46.2 (31-65)	85.3 (66.2-108.3)	12 men, 2 women

Table II Pregabalin Dosing Paradigm in Study 2

		Dose		
Weeks	Group	Day 1	Days 8-21	Day 22
	Group 1			
1-4	4 Subjects	25 mg	25 mg every 8 h	25 mg
	1 Subject	Placebo	Placebo every 8 h	Placebo
	Group 2			
5-8	6 Subjects	25 mg	25 mg every 8 h	25 mg
	2 Subjects	Placebo	Placebo every 8 h	Placebo
	Group 3			
9-12	6 Subjects	100 mg	100 mg every 8 h	100 mg
	2 Subjects	Placebo	Placebo every 8 h	Placebo
	Group 4			
13-16	5 Subjects	200 mg	200 mg every 8 h	200 mg
	1 Subject	Placebo	Placebo every 8 h	Placebo
	Group 5			
17-20	8 Subjects	200 mg	200 mg every 8 h	200 mg
	2 Subjects	Placebo	Placebo every 8 h	Placebo
	Group 6			
21-24	8 Subjects	300 mg	300 mg every 12 h	300 mg
	2 Subjects	Placebo	Placebo every 12 h	Placebo
	Group 7			
25-28	8 Subjects	300 mg	300 mg every 8 h	300 mg
	2 Subjects	Placebo	Placebo every 8 h	Placebo

6 treatment sequences (2 subjects per sequence). For treatment 1, capsules were administered with 8 oz of water. For treatment 3, capsules were administered with 4 oz of the low-fat milk provided with the breakfast. The breakfast was consumed in 25 minutes and consisted of cereal, 2 eggs scrambled without fat, 2 slices of white toast spread with 2 teaspoons of margarine, and 8 oz of low-fat (2%) milk. Blood samples were collected before and 0.17, 0.33, 0.50, 0.67, 0.83, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 60 hours following each treatment.

The second food-effect study (study 5) was an open-label, single-dose, randomized, 2-way crossover in which the effect of a high-fat breakfast was assessed. On 2 occasions, 7 days apart, 14 subjects received the following treatments in random order: (1) one 150-mg pregabalin capsule after an overnight fast; and (2) one 150-mg pregabalin capsule taken immediately following completion of a 1000-kcal high-fat breakfast. In treatment 1, the capsule dose was administered with 6 oz of water. In treatment 2, the capsule dose was administered with 6 oz of water within 5 minutes following completion of the meal. In treatment 2, the study medication was taken when subjects completed a high-fat breakfast, 20 minutes after starting the breakfast. The high-fat breakfast consisted of 2 eggs scrambled in butter, 2 pieces of bacon, 4 oz of hash-brown potatoes, 2 pieces of white toast spread with 2 teaspoons of butter, and 8 oz of whole milk. Blood samples were collected before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, 36, and 48 hours after the dose on days 1 and 8.

For both studies, subjects were required to fast overnight (at least 8 hours) before dosing. Subjects receiving doses under fasting conditions remained fasting for 4 hours following each dose except for 6 oz of unsweetened juice or water provided after

the 2-hour blood collection. Subjects receiving doses under fed conditions also received 6 oz of unsweetened juice or water after the 2-hour blood sample was withdrawn. Identical lunches and identical dinners were served to all treatment groups following collection of the 4- and 10-hour blood samples, respectively. No other food or beverage (except water) was allowed until after the 12-hour blood collection. Capsules were swallowed intact.

Sample Handling and Determination of Plasma and Urine Pregabalin Concentrations

All blood samples were collected in glass tubes containing heparin. Following centrifugation, plasma samples were transferred to plastic tubes and stored frozen at –20°C until assayed for pregabalin. The predose 100-mL urine samples and a 20-mL aliquot of urine from each postdose collection interval were stored frozen at –20°C until analyzed for pregabalin concentration.

Pregabalin concentrations in plasma and urine samples from active treatments were assayed by a validated high-performance liquid chromatography method with UV absorbance detection. The method was a modification of a previously published method.[25,29] An internal standard, 1-(aminomethyl) cycloheptaneacetic acid (PD 403609), was included in all assays. Plasma samples were deproteinized with perchloric acid. Urine and deproteinized plasma samples were derivatized at room temperature with 2,4,6-trinitrobenzenesulfonic acid under alkaline conditions. The reaction was terminated with hydrochloric acid, and the derivatized analytes were extracted with cyclohexane. The organic phase was evaporated to dryness at 50°C, and the residue was reconstituted in mobile phase. Separation was achieved using a 3-µm Supelco custom-packed column (Supelcosil LC-18-DB) with an aqueous acetonitrile mobile phase. Absorbance was monitored at 350 nm. Quantification of pregabalin concentrations was based on peak-height ratios.

The plasma assay method was validated for 2 analytical ranges, with lower limits of quantitation of 0.005 µg/mL for a 1.0-mL sample volume and 0.05 µg/mL for a 0.5-mL sample volume. The urine method was validated with a lower limit of quantitation of 0.06 µg/mL for a 0.5-mL sample volume. Precision of calibration and quality control standards assayed during sample analysis, expressed as percent relative standard deviation (%CV), was 12.3% or less for plasma and 6.2% or less for urine. Accuracy of mean concentrations in quality control samples, expressed as percent error relative to nominal values, ranged from –6.2% to 8.0% for plasma samples and from –6.8% to 7.1% for urine samples. Standard curves were linear over the calibration ranges (0.005-2.0 µg/mL or 0.05-20.0 µg/mL for plasma and 0.06-20.0 µg/mL for urine). A more detailed description of the analytical procedure is described by Windsor and Radulovic.[29]

Pharmacokinetics and Statistical Analyses

Pregabalin pharmacokinetic parameter values were calculated using noncompartmental analysis of plasma and urine concentration–time data. Maximum plasma concentration (C_{max}) and the time it occurred (t_{max}) were recorded as observed. Area under the plasma concentration–time curve (AUC) values were estimated using the linear trapezoidal rule. Values for $AUC_{0\text{-}tlqc}$ were calculated from time 0 to time of the last quantifiable concentration (tlqc). Values for $AUC_{0\text{-}\tau}$ were calculated from time 0 to τ hours after the dose, where τ is the dosing interval (8 or 12 hours). Terminal elimination rate constant (λz) values were estimated as the absolute value of the slope of a linear regression of natural logarithm (ln) of concentration on time during the terminal phase of the concentration–time profile. Elimination half-life ($t_{1/2}$) values were calculated as $\ln(2)/\lambda z$. $AUC_{0\text{-}\infty}$ values were calculated as the sum of corresponding $AUC_{0\text{-}tlqc}$ and $lqc/\lambda z$ values.

Oral apparent clearance (CL/F) values were calculated as $\frac{\text{Dose}}{\text{AUC}(0-\infty)}$ following administration of a single dose and as $\frac{\text{Dose}}{\text{AUC}(0-\tau)}$ at steady state. Apparent volume of distribution values (Vd/F) were calculated as $\frac{\text{CL/F}}{\lambda z}$. Observed accumulation was assessed by calculation of the ratio of C_{max} values, concentrations at the end of a dosing interval (C8 or C12), and $AUC_{0\text{-}8}$ or $AUC_{0\text{-}12}$ values at steady state to the corresponding values after a single dose. Theoretical accumulation ratio was calculated as $\frac{1}{(1-e^{-\lambda_z \tau})}$, where λ_z was obtained from single-dose data.

Amount of unchanged pregabalin in urine (Ae) was calculated from urinary pregabalin concentrations and urine volumes. For single-dose administration, Ae was calculated from time 0 to 60 hours following the dose. Individual Ae values for the 48- to 60-hour urine collections corresponded to

1% or less of administered dose, indicating that urinary excretion was essentially complete 60 hours after the dose. For multiple-dose administration, Ae was calculated from 0 to τ hours postdose. Percentage of dose excreted as unchanged pregabalin in urine (Ae%) was calculated as (Ae/Dose) × 100. Pregabalin renal clearance (CL_r) following single-dose administration was calculated as Ae/$AUC_{0-\infty}$. Owing to the number of subjects with observed Ae% values greater than 110%, CL_r was not calculated following multiple dosing.

Standard statistical techniques (arithmetic mean and percent coefficient of variation [%CV]) were used to assess pharmacokinetic parameters in studies 1 to 3. For the food-effect studies, parameter values (including natural logarithms of C_{max} [ln(C_{max})] and AUC [ln(AUC)] values) were evaluated by analysis of variance (ANOVA), using a model incorporating subject, treatment, sequence, and period effects. Statistically significant *(P* < .05) sequence and period effects were assessed using subject within sequence mean square error (MSE) and residual error variance, respectively. Least-squares mean pharmacokinetic parameter values and back-transformed values of least-squares mean ln(C_{max}) and ln(AUC) values (analogous to geometric means) were obtained from the ANOVA. For comparisons of interest, ratios of least-squares treatment mean values were calculated, and associated 90% confidence intervals were determined for upper limits and lower limits for untransformed parameters, where $\overline{X}_{TEST} - \overline{X}_{REF}$ is the estimate of the difference between treatment least-squares mean values for the test treatment ($\overline{X}_{TEST}$) and the reference ($\overline{X}_{REF}$), and SE is the standard error of the difference estimate. The value $t_{0.95,}\nu$ is the critical value from the 95th percentile of the Student's *t* distribution, with ν degrees of freedom associated with the MSE term, and is equivalent to the two 1-sided tests.[30,34] Absence of a clinically important effect of food on the pharmacokinetics of pregabalin would be concluded if the 90% confidence interval for AUC was contained within the 80% to 125% range.

Because no biomarkers or efficacy parameters were readily available in phase I studies to investigate pharmacokinetic/pharmacodynamic relationships, exploration of such relationships were not a part of this study plan. The initial oral dose of 1 mg in study 1 was 1/90 of the oral median effective dose (ED_{50}; 1.8 mg/kg) estimated from rat models considered predictive of efficacy in patients with epilepsy. Single oral doses of pregabalin were to be cautiously escalated to a maximum dose of 600 mg or a C_{max} concentration of 9.7 μg/mL (known to engender no adverse events in the most sensitive toxicology species). No significant adverse events (including ataxia) are known at lower doses.

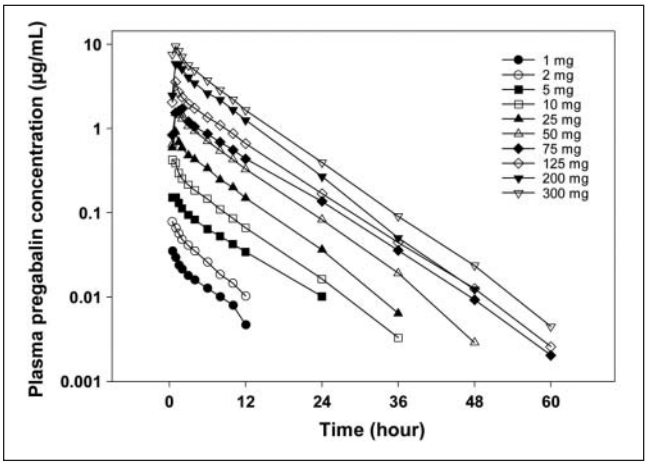

Figure 1. Mean plasma pregabalin concentration-time profiles following single-dose administration in study 1 (n = 3 subjects/dose, except for n = 2 subjects/2-mg dose).

RESULTS

Single-Dose Pharmacokinetics

Pregabalin was rapidly absorbed following oral administration of single 1-mg to 300-mg doses, with mean t_{max} values ranging from 0.7 to 1.3 hours (Tables III and IV). Following a very short distribution phase, plasma concentrations declined monoexponentially over the 60-hour observation period (Figure 1). Mean C_{max} and $AUC_{0-\infty}$ values were proportional to dose (Figure 2). Mean elimination $t_{1/2}$ values ranged from 4.6 to 6.8 hours and were independent of dose (Tables III and IV). Pharmacokinetic variability, assessed by the %CV for the pharmacokinetic parameters, was very low for pregabalin (Tables III and IV).

Percentage of dose excreted unchanged in urine was independent of dose and averaged approximately 90% (Tables III and IV). The percent of dose in the urine is an excellent measure of pregabalin oral bioavailability because less than 0.1% of an orally administered, radiolabeled dose was recovered in the feces and 98% of the radioactivity recovered in the urine was unchanged pregabalin.[35] Therefore, based on urine pregabalin data, mean oral bioavailability was approximately 90% after 1- to 300-mg single, oral doses. Mean pregabalin CL_r following single-dose administration was

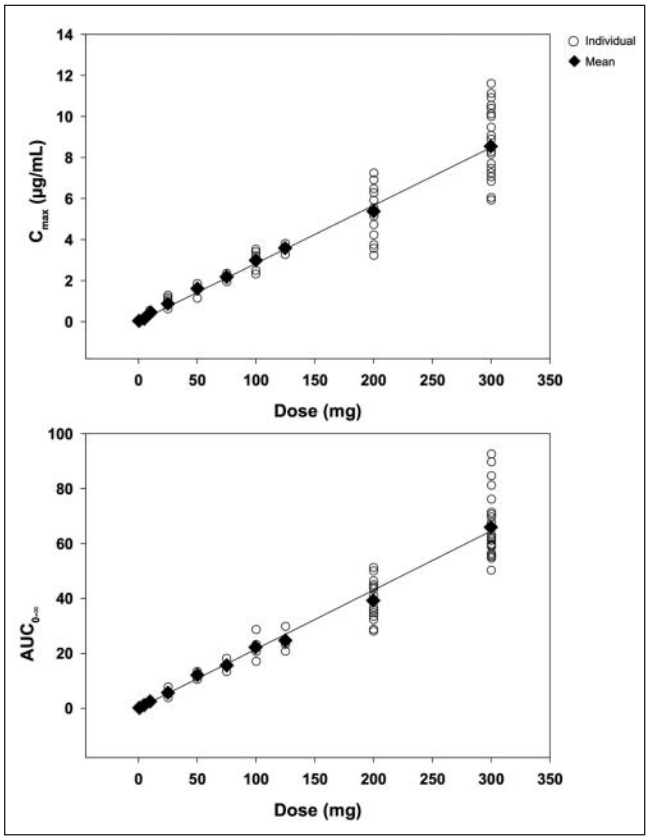

Figure 2. Individual and mean single-dose pregabalin maximum observed plasma pregabalin concentration (C_{max}; upper panel) and area under plasma pregabalin concentration–time curve from 0 to infinite time ($AUC_{0-\infty}$; lower panel) values in healthy subjects from studies 1 to 3 plotted as a function of dose. Line represents regression through individual data, forced through origin.

independent of dose and ranged from 58.0 to 80.9 mL/min (Tables III and IV). These values were essentially equivalent to apparent systemic clearance values (57.6-82.0 mL/min) after correcting for oral bioavailability. Average apparent Vd/F for pregabalin was approximately 36 L after correcting for oral bioavailability (Tables III and IV).

Multiple-Dose Pharmacokinetics

Accumulation of plasma pregabalin concentrations following administration every 8 and 12 hours for 2 or 4 weeks was consistent with pregabalin elimination $t_{1/2}$ and was predictable from single-dose data (Table IV). Theoretical average accumulation ratio ranged from 1.62 to 1.76 following administration every 8 hours and was 1.40 following administration every 12 hours. Observed mean accumulation ranged from 1.48 to 2.03 after every 8-hour dosing and from 1.21 to 1.50 after every 12-hour dosing. Steady state was achieved within 24 to 48 hours after the start of repeated dose administration (Figure 3). Elimination $t_{1/2}$ values ranged from 5.5 to 6.7 hours, were independent of dose, and were unaffected by repeated administration. Mean steady-state C_{max} and AUC values increased in proportion to dose (Table IV).

Following multiple-dose administration, mean Ae% values were, in general, slightly higher than single-dose values and were independent of dose (Table IV). Data from 8 subjects whose values were more than 110% following multiple-dose administration were included in the means. These values may have resulted from inaccuracies in urine collection, such as failure of subjects to void completely before the start of the 0- to 4-hour collection interval.

Effect of Food on the Pharmacokinetics of Pregabalin

In study 5, 1 subject received treatment only in the first period; therefore, data from this subject were omitted from the statistical analysis. No statistically significant sequence or period effects were observed following ANOVA evaluation of pharmacokinetic parameters from the 2 food-effect studies. When a 100-mg pregabalin capsule was administered with a standard breakfast, t_{max} was delayed 2.6 hours and mean C_{max} was reduced by 31% relative to fasting administration (Table V). Extent of availability, represented by mean $AUC_{0-\infty}$ values, was similar in the fed and fasted states, with the 90% confidence interval for the ratio falling within 80% to 125% (Table V). Elimination $t_{1/2}$ values were also similar in the fed and fasted states (Table V).

DISCUSSION

Single doses of pregabalin were generally well tolerated by healthy subjects. There were no deaths, serious adverse events, or withdrawals due to adverse events. No clinically significant changes were observed in physical examinations, ophthalmic examinations, vital sign measurements, clinical laboratory measurements, or cardiac measurements. One subject was discontinued from study 3 for mildly elevated pancreatic enzymes. The principal investigator judged the elevated pancreatic enzymes to be related

Table III Mean (%CV) Pregabalin Pharmacokinetic Parameters in Healthy Subjects (n = 3/Group) Following Single Oral Doses of Pregabalin 1, 2, 5, 10, 25, 50, 75, 125, 200, or 300 mg

Dose, mg	Formulation	C_{max}, μg/mL	t_{max}, h	Terminal Elimination $t_{1/2}$, h	$AUC_{0-\infty}$, μg·h/mL	CL/F, mL/min	Vd/F, L	Ae, %	CL_r, mL/min
1	Solution	0.0383 (10.1)	0.7 (43.3)	5.7 (13.9)	0.223 (13.5)	75.6 (14.4)	37.0 (1.0)	92.4 (7.3)	69.5 (10.8)
2	Solution	0.0848[a] (NC)	0.8[a] (NC)	4.6[a] (NC)	0.428[a] (NC)	77.9[a] (NC)	30.7[a] (NC)	88.8[a] (NC)	69.1[a] (NC)
5	Capsule	0.156 (12.9)	0.9 (20.7)	6.8 (17.0)	1.24 (11.8)	68.2 (11.6)	40.2 (22.9)	88.9 (2.3)	60.5 (9.4)
10	Capsule	0.459 (14.7)	0.8 (34.6)	6.0 (9.4)	2.54 (13.8)	66.4 (14.5)	34.7 (21.9)	86.8 (11.2)	58.0 (22.2)
25	Capsule	0.918 (21.5)	1.0 (0.0)	5.6 (16.6)	5.83 (12.7)	72.2 (13.2)	34.7 (18.3)	85.8 (10.7)	61.5 (7.8)
50	Capsule	1.61 (25.7)	1.2 (23.3)	5.8 (16.0)	12.2 (11.9)	69.0 (13.0)	35.3 (29.6)	89.5 (2.7)	61.8 (13.5)
75	Capsule	2.18 (8.9)	1.3 (43.3)	6.6 (11.7)	15.6 (15.5)	81.4 (15.3)	45.7 (4.1)	94.3 (6.2)	77.2 (20.8)
125	Capsule	3.59 (8.0)	1.0 (0.0)	5.8 (26.7)	24.6 (19.1)	86.8 (17.8)	42.9 (17.8)	89.7 (0.6)	77.9 (18.2)
200	Capsule	5.96 (11.7)	1.2 (24.7)	5.2 (13.5)	46.0 (17.6)	74.2 (19.4)	33.0 (4.6)	91.8 (6.2)	68.5 (24.7)
300	Capsule	9.46 (11.0)	0.8 (34.6)	5.6 (17.1)	66.3 (6.8)	75.6 (7.2)	36.3 (13.9)	89.9 (3.9)	68.0 (10.0)

C_{max}, maximum observed plasma pregabalin concentration; t_{max}, time of maximum observed plasma pregabalin concentration; $t_{1/2}$, half-life; $AUC_{0-\infty}$, area under plasma pregabalin concentration–time curve from 0 to infinite time; CL/F, apparent oral clearance; Vd/F, apparent volume of distribution; Ae, total amount of unchanged pregabalin excreted in urine within 60 hours postdose, expressed as percentage of dose; CL_r, renal clearance; NC, not calculated.
[a]n = 2.

Table IV Summary of Mean (Percent Relative Standard Deviation) Pregabalin Pharmacokinetic Parameter Values Following Single- and Multiple-Dose Administration (Studies 2 and 3)

Dose, mg	Dosing Regimen	n	C_{max}, μg/mL	t_{max}, h	Terminal Elimination $t_{1/2}$, h	AUC, μg h/mL	CL/F, mL/min	Vd/F, mL/min	Ae, %	CL_r, mL/min
Single dose										
25	—	10	0.864 (19.3)	0.850 (28.4)	5.48 (18.1)	5.63 (21.6)	77.3 (22.5)	35.8 (18.5)	87.7 (13.8)	67.0 (20.6)
100	—	6	2.99 (16.2)	0.833 (31.0)	6.10 (18.0)	22.1 (16.8)	77.0 (16.4)	40.0 (13.0)	90.2 (8.4)	69.3 (15.2)
200	—	13	5.23 (27.0)	1.31 (33.3)	6.13 (13.7)	37.7 (16.3)	90.8 (17.1)	48.3 (21.5)	90.6 (21.1)	80.9 (23.4)
300	—	8	8.59 (17.4)	1.00 (26.7)	6.62 (13.1)	71.4 (14.4)	71.2 (13.3)	41.0 (20.6)	96.9 (13.0)	68.8 (16.6)
300	—	8	7.57 (16.4)	1.38 (57.5)	6.64 (10.1)	62.8 (9.3)	80.3 (9.5)	46.0 (10.5)	91.2 (4.8)	73.2 (9.8)
300	—	12	8.99 (18.5)	1.00 (21.3)	6.01 (15.5)	64.1 (19.8)	80.4 (16.7)	41.4 (19.4)	ND	ND
Steady state										
25	every 8 h	8	1.39 (19.5)	0.938 (34.2)	5.94 (17.3)	6.67 (18.3)	64.1 (16.1)	32.4 (13.8)	94.3 (22.6)	NC
100	every 8 h	6	5.03 (21.3)	0.833 (31.0)	6.31 (19.6)	25.2 (23.0)	68.9 (20.9)	36.6 (11.6)	108.0 (11.6)	NC
200	every 8 h	11	8.52 (14.8)	0.909 (22.2)	6.27 (13.6)	41.7 (12.8)	81.0 (11.7)	43.7 (13.7)	82.0[a] (30.6)	NC
300	every 8 h	8	13.4 (14.5)	1.00 (26.7)	6.45 (13.3)	67.4 (15.4)	85.1 (6.4)	49.1 (14.2)	99.3 (11.9)	NC
300	every 12 h	8	9.07 (10.5)	1.44 (57.1)	6.70 (16.2)	59.0 (6.4)	75.8 (15.4)	42.5 (21.2)	91.2 (14.6)	NC
300	every 8 h[b]	12	13.2 (16.8)	1.08 (43.3)	6.55 (11.2)	67.4 (14.5)	75.6 (14.4)	42.8 (17.4)	ND	ND

All steady-state values obtained after 2 weeks of dosing, except where noted. C_{max}, maximum observed plasma pregabalin concentration; t_{max}, time of maximum observed plasma pregabalin concentration; $t_{1/2}$, half-life; AUC, area under plasma pregabalin concentration–time curve from 0 to infinite time following a single dose of administration from time 0 to 8 hours postdose following administration every 8 hours or from time 0 to 12 hours postdose following administration every 12 hours; CL/F, apparent oral clearance; Vd/F, apparent volume of distribution; Ae, total amount of pregabalin excreted in urine for 60 hours postdose on day 1 or over the dosing interval on days 22 and 29; CL_r, renal clearance; ND, not determined; NC, not calculated.
[a]n = 9.
[b]4 weeks of dosing.

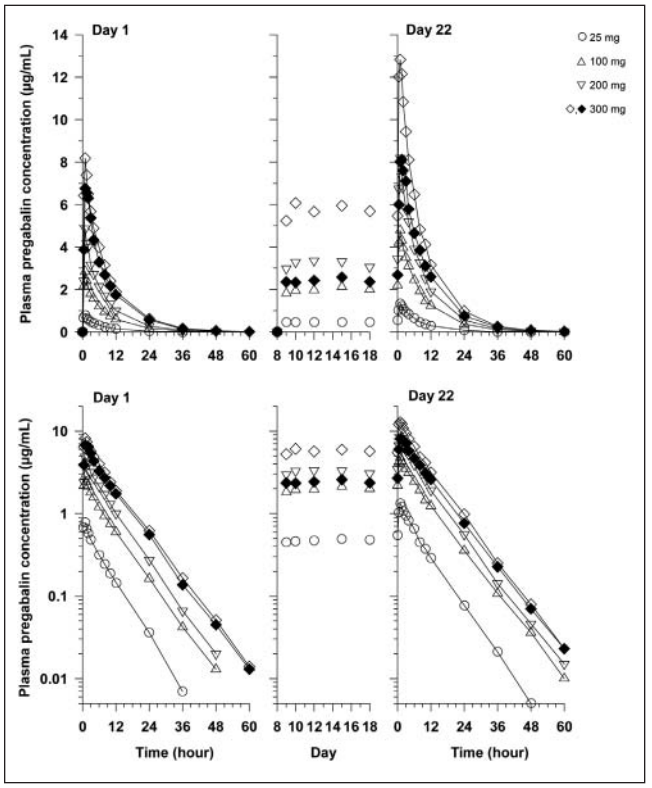

Figure 3. Mean plasma pregabalin concentration–time profiles following administration of single (25, 100, 200, and 300 mg) pregabalin doses on day 1; mean morning predose plasma pregabalin concentrations following the same doses every 8 hours (open symbols) or every 12 hours (closed symbols) beginning on day 8; and mean plasma pregabalin concentration–time profiles following administration of the final dose on day 22. Linear and semilogarithmic scales shown on upper and lower panels, respectively.

to a preexisting condition and unlikely related to pregabalin. Pregabalin multiple dose administration was likewise generally well tolerated by healthy volunteers after 2 or 4 weeks of administration, and no deaths or serious adverse events were reported. The most common adverse events involved nervous and digestive system function and were all mild to moderate. Overall, the most frequently reported adverse events during pregabalin administration were dizziness and somnolence.

In healthy volunteers, pregabalin was rapidly and well absorbed, with an absolute bioavailability of approximately 90% based on recovery of unchanged drug in urine. Systemic exposure to pregabalin was proportional to dose over a range of 1 to 300 mg administered as single doses and a range of 25 mg every 8 hours to 300 mg every 8 hours at steady state. Steady-state exposure to pregabalin was predicted from single-dose administration, indicating that pregabalin pharmacokinetics is independent of time.

Daily systemic exposure for pregabalin 600 mg/d given every 12 hours and every 8 hours was similar, indicating that frequency of drug administration had no effect on pregabalin pharmacokinetics. Administration of pregabalin capsules with food reduced the rate, but not the extent, of systemic pregabalin availability.

The effect on bioavailability of 150-mg pregabalin administration with a high-fat breakfast was similar to that observed with a standard breakfast. As shown in Table V, mean t_{max} was delayed by approximately 1 hour and mean C_{max} was reduced by 25% compared with values observed in the fasting state. The mean $AUC_{0-\infty}$ value with food was approximately 7% lower than the fasting value, but the 90% confidence interval for the ratio fell within 80% to 125%. Mean $t_{1/2}$ values for the 2 treatments were similar.

These results are consistent with slower delivery of the drug to the sites of absorption in the intestine due to a food-induced delay in gastric emptying.[36,37] Furthermore, preclinical[38] and clinical[35] results suggest that because there is a slight delay between onset of efficacy and significant plasma pregabalin concentrations in epilepsy and neuropathic pain models, AUC and not C_{max} is a better predictor of pregabalin efficacy. Reductions in rate, accompanied by a similar extent of drug absorption, are expected to have a minimal impact on clinical effects. Therefore, it may be suggested that pregabalin capsules can be administered without regard to meals.

Study 4 investigated the bioavailability of the immediate-release pregabalin capsules relative to a pregabalin solution. Both rate and extent of pregabalin absorption following capsule administration were bioequivalent to the pregabalin solution. After correcting for oral bioavailability, the estimated volume of distribution for pregabalin was approximately 36 L, suggesting that pregabalin is predominately distributed throughout total body water.[39] This is consistent with its negative log P, high water solubility, and negligible plasma protein binding.[40] After correcting for oral bioavailability, systemic clearance values are essentially equivalent to CL_r values, suggesting pregabalin is subject to little, if any, extrarenal systemic elimination. The mean elimination $t_{1/2}$ of pregabalin in healthy volunteers averaged 6.3 hours. Because CL_r of pregabalin is less than glomerular filtration rate (approximately 125 mL/min in healthy normal volunteers) and pregabalin is not bound to plasma proteins,

Table V Pregabalin Pharmacokinetic Parameter Values Following Administration of Capsules to Fasting Subjects and to Subjects Fed a Standard (Study 4) or High-Fat (Study 5) Breakfast

Parameter	Treatment Mean Parameter Values		Ratio (Test/Reference)	90% Confidence Interval
	Fed (Test)	Fasting (Reference)		
Standard breakfast, dose = 100 mg (n = 11)				
C_{max}, μg/mL	2.59	3.78	68.6	64.0-73.6
t_{max}, h	3.17	0.615	515.0	Not applicable
$AUC_{0\text{-}tlqc}$, μg·h/mL	25.3	26.6	94.8	91.8-97.9
$AUC_{0\text{-}\infty}$, μg·h/mL	25.4	26.7	94.9	92.0-98.0
Terminal elimination $t_{1/2}$, h	6.61	6.92	95.5	85.9-105.0
High-fat breakfast, dose = 150 mg (n = 14)				
C_{max}, μg/mL	2.60	3.47	74.8	68.0-82.2
t_{max}, h	2.29	1.25	183.0	Not applicable
$AUC_{0\text{-}tlqc}$, μg·h/mL	24.3	26.2	92.6	90.4-94.9
$AUC_{0\text{-}\infty}$, μg·h/mL	25.5	27.3	93.3	91.4-95.2
Terminal elimination $t_{1/2}$, h	6.72	6.70	100.0	96.5-104.0

Ratio, ratio of treatment mean values, expressed as a percentage (100% × test/reference); 90% confidence interval, 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percent of the reference mean; C_{max}, maximum observed plasma pregabalin concentration; t_{max}, time of maximum observed plasma pregabalin concentration; $AUC_{0\text{-}tlqc,}$ area under plasma pregabalin concentration–time curve from 0 to time of last quantifiable concentration; $AUC_{0\text{-}\infty}$, area under plasma pregabalin concentration–time curve from 0 to infinite time; $t_{1/2}$, half-life.

renal elimination is characterized by net tubular reabsorption. Therefore, renal function is an important determinant of pregabalin elimination; and dose adjustment is necessary in patients with medically significant renal impairment.[41]

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