CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-397
21-423
21-424

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-397	Submission Date(s): August 7, 2001	
Brand Name	Neurontin	
Generic Name	Gabapentin	
Reviewer	Sandip K. Roy, Ph.D.	
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OCPB Division	DPE2	
OND division	Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170	
Sponsor	Pfizer, Ann Arbor, Michigan	
Relevant IND(s)		
Submission Type; Code	6S	
Formulation; Strength(s)	Capsules:	100, 300,& 400 mg
	Tablets:	600 & 800 mg
	Oral Solutions:	250 mg/5 mL
Indication	Management of [redacted] postherpetic neuralgia	

1 Executive Summary

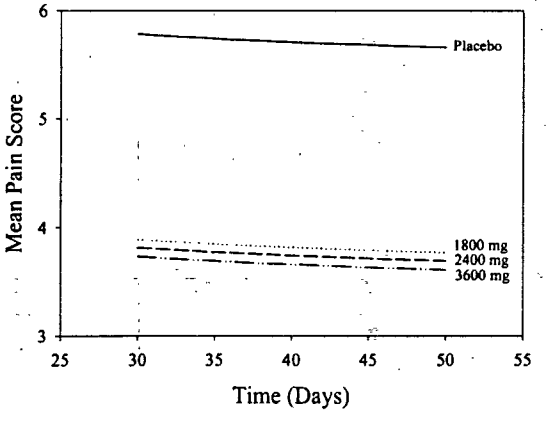
Gabapentin is an anticonvulsant approved in the United States in 1993 for use in adult patients with partial epilepsy. It is structurally related to gamma-aminobutyric acid (GABA), a neurotransmitter that plays a role in pain transmission and modulation. The mechanism by which gabapentin exerts its pharmacological actions is unknown. The proposed dosing regimen in adults with [redacted] postherpetic neuralgia is as follows: gabapentin therapy may be initiated as a single 300 mg dose on Day 1, 600 mg/day (in 2 divided doses) on Day 2, and 900 mg/day (in 3 divided doses) on Day 3. The dose can subsequently be titrated up as needed for pain relief to a maximum daily dose of 3600 mg (in 3 divided doses).

The proposed maximum daily dose of 3600 mg/day for management of [redacted] postherpetic neuralgia is higher than the maximum dose recommended for epilepsy (1800 mg/day) in the current labeling. Thus, a clinical pharmacology study was conducted to assess the dose-proportionality of steady-state plasma gabapentin concentrations in healthy adult subjects at doses up to 4800 mg/day. Peak plasma gabapentin concentrations occur 3 to 4 hours postdose following a single oral dose of

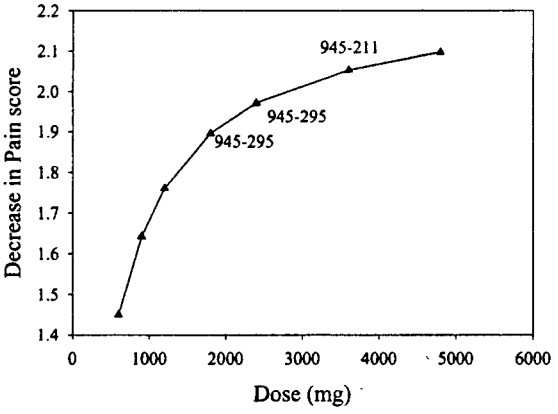
gabapentin. Steady-state plasma gabapentin concentrations increased with dose over a 1200 to 4800 mg/day (given every 8 hours) dose range, but increases were less than dose-proportional. The lack of dose-proportionality was due to a decrease in gabapentin absolute bioavailability with increasing dose. Absolute bioavailability of gabapentin was approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day, given in divided doses q8h, respectively. While food increased the absolute bioavailability of gabapentin (14% with a high-fat meal), the increases in plasma gabapentin concentrations do not warrant dosage adjustment.

Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after administration of 150 mg intravenous administration is 58 L. Gabapentin was eliminated from the systemic circulation by renal excretion of unchanged drug. Gabapentin is not appreciably metabolized in humans. Gabapentin half-life and systemic clearance values were independent of dose and not altered following repeated administration. Gabapentin half-life was approximately 5 to 7 hours in healthy subjects. Following intravenous administration, gabapentin plasma and renal clearances were approximately equal to creatinine clearance.

A population analysis was performed to describe the exposure-response relationship of gabapentin following multiple doses in patients in the two pivotal postherpetic neuralgia clinical studies. The initial, proof of efficacy study (945-211) was conducted at the dose of 3600 mg/day in patients who were experiencing pain for more than 3 months after healing of the acute herpes zoster rash. The second study (945-295) was a confirmatory study, that included 2 doses of gabapentin, 1800 or 2400 mg/day. This study had similar inclusion criteria for postherpetic neuralgia as the study 945-211. In these studies, the initial gabapentin treatment was 300 to 900 mg/day with titration over 3 to 4 weeks to final dose dependent upon the study protocol. Following titration, the dose was kept constant for the duration of the study. The overall steady state dose range investigated was 1800 to 3600 mg/day. At steady state, gabapentin effect was best described by an E_{max} model using daily gabapentin dose corrected for estimated bioavailability. Following are the simulation expectations for pain score during the fixed dose period at 1800, 2400 and 3600 mg using the parameters from the final model:



Parameter estimates from the final model were used to obtain the following plot, which suggest that gabapentin effect increased with dose in a nonlinear fashion.



Gender had no clinically relevant effect on the exposure-response model. In the postherperpetic neuralgia trials the population was homogeneously aged, thus, inclusion of age (modeled as a continuous covariate) did not result in a significant improvement in the fit and was not included in the model.

Gabapentin pharmacokinetics have been explored in several special populations. Gabapentin pharmacokinetic parameters in epilepsy patients are identical to those in healthy subjects. Elderly subjects do not require dosage adjustment unless renal function is sufficiently compromised. Gender does not appear to affect gabapentin pharmacokinetics as pharmacokinetic parameters for males and females are similar. Pharmacokinetic differences due to race have not been studied. Because gabapentin does not undergo appreciable metabolism, no studies have been performed in patients with hepatic impairment. In adult subjects with renal insufficiency, mean half-life ranged from 6.5 hours for subjects with creatinine clearance (CLcr) >60 mL/min to 52 hours for subjects with CLcr <30 mL/min. Since gabapentin renal clearance was proportional to CLcr, CLcr can be used to adjust gabapentin doses in patients with renal impairment. Hemodialysis effectively removed gabapentin from plasma and decreased gabapentin half-life in hemodialysis subjects from 132 (while not on dialysis) to 3.8 hours (during dialysis.

Based on *in vitro* studies conducted with gabapentin, a metabolically-based interaction between gabapentin and a drug whose clearance is dependent upon the major cytochrome P450 enzymes is highly unlikely at plasma concentrations associated with doses up to 3600 mg/day (C_{max} 11.6 µg/mL), the highest recommended daily dose.

[redacted]. According to literature, when a 60 mg controlled release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. The authors of this article suggested that changes in gabapentin pharmacokinetics might have been caused by morphine-induced reduction in gastrointestinal motility, resulting in increased time for gabapentin absorption. Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine.

1.1 Recommendation

This NDA is acceptable from OCPB perspective.

2 Table of Contents

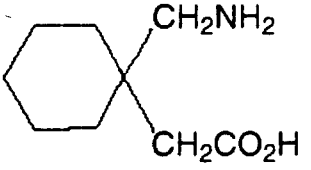
3 Summary of CPB Findings

4 QBR

4.1 General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Gabapentin is described as 1-(aminomethyl)cyclohexaneacetic acid with an empirical formula of $C_9 H_{17}NO_2$ and a molecular weight of 171.24. The molecular structure of gabapentin is:



Gabapentin is a white to off-white crystalline solid. It is freely soluble in water and both basic and acidic aqueous solutions.

Neurontin (gabapentin) capsules, Neurontin (gabapentin) tablets, and Neurontin (gabapentin) oral solution are supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin, elliptical film-coated tablets containing 600 mg and 800 mg of gabapentin or an oral solution containing 250 mg/5 mL of gabapentin.

The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100 mg capsule shell contains gelatin and titanium dioxide. The 300 mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400 mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide.

The inactive ingredients for the tablets are poloxamer 407, copolyvidonum, cornstarch, magnesium stearate, hydroxypropyl cellulose, talc, candelilla wax and purified water.

The inactive ingredients for the oral solution are glycerin, xylitol, purified water and artificial cool strawberry anise flavor.

What is the proposed mechanism of drug action and therapeutic indications?

The mechanism by which gabapentin exerts its pharmacological actions is unknown. In animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). In particular, gabapentin prevents pain-related responses in several models of neuropathic pain in rats or mice.

The proposed therpeutic indication for gabapentin is the management of [redacted]

What is the proposed dosage and route of administration?

The sponsor has proposed the following dosing regimen:

In adults [redacted] with postherpetic neuralgia, gabapentin therapy may be initiated as a single 300 mg dose on Day 1, 600 mg/day (in 2 divided doses) on Day 2, and 900 mg/day (in 3 divided doses) on Day 3. The dose can subsequently be titrated up as needed, [redacted] to a maximum daily dose of 3600 mg (in 3 divided doses).

Route of administration oral.

What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutic study data (e.g., if disparate efficacy measurements or adverse event reports can be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?

The sponsor has created a data set from the 5 clinical studies. The data set included subject identification, daily pain scores, gabapentin dose, and demographic and physiologic parameters. Individual daily pain scores, recorded during the baseline, titration, and double-blind phases of the study using an 11-point Likert scale (0 = no pain to 10 = worst possible pain), were used for analysis. The use of individual daily pain scores allowed investigation of temporal effects (onset and duration of effect) whereas the primary efficacy endpoint (mean of the last 7 daily pain scores while on study medication) did not. Further, the number of observed individual daily pain scores would likely afford more power to detect significant covariates of response. A subject-specific random-effects model was used to characterize the relationship between daily pain score and gabapentin exposure in individual patients, taking into account placebo effect. Covariates such as age, gender, and mean baseline pain score were tested to determine the impact of these factors on the exposure-response relationship.

4.2 General Clinical Pharmacology

What are the characteristics of the exposure-response relationships (dose-response, concentration-response)?

Two separate exposure response analyses were performed. The first was a population analysis in patients from five clinical studies to describe the exposure-response relationship of gabapentin following multiple doses, and to identify the factors that may affect this relationship. The second population analysis was performed to describe the exposure-response relationship of gabapentin following multiple doses in patients in the two pivotal postherpetic neuralgia clinical studies.

In these studies, the initial gabapentin treatment was 300 to 900 mg/day with titration over 3 to 4 weeks to final dose dependent upon the study protocol. Following titration, the dose was kept constant for the duration of the study. The overall steady state dose range investigated was 600 to 3600 mg/day.

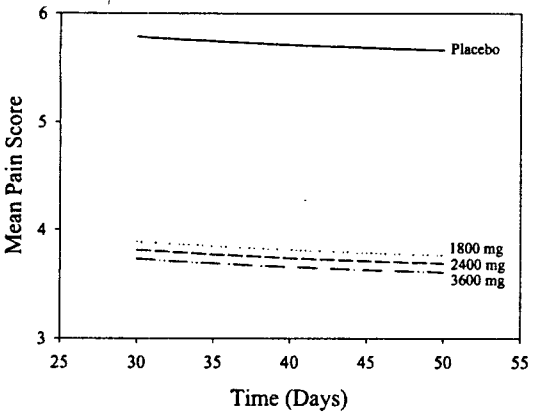
- The results suggest that gabapentin effect increased with dose in a nonlinear fashion.
- Increasing age (possibly related to an age associated decrease in renal function resulting in an increase in steady state concentration of gabapentin) increased response to gabapentin.
- Gender had no clinically significant effect on the exposure-response model.

Following table summarizes the population parameter estimates of the final model of exposure-response relationship of gabapentin in the five clinical studies:

Parameter (units)	Estimate (95% CI)
Placebo Effect	
Immediate Placebo Response (pain score units)	0.247 (0.16, 0.33)
Time-Dependent Placebo Response	
Maximum Magnitude (pain score units)	1.28 (1.00, 1.55)
Rate Constant (day^{-1})	0.048 (0.038, 0.059)
Fraction Change for Studies 945-211 and -295	-0.353 (-0.568, -0.139)
Fraction Change for Study 945-224	0.222 (0.06, 0.32)
Fraction Change for Studies 945-210 and -306	0 Fixed
Baseline Effect (Pain Score Units)	-0.0227 (-0.037, -0.011)
Drug Effect	
Maximal Drug Effect (Pain Score Units)	2.26 (0.880, 3.64)
Amount Absorbed at Half the Maximal Drug Effect (mg Absorbed per Day)	1920 (116, 3724)
Fractional Change in Exposure per Unit Change in age From 65	0.023 (0.012, 0.035)

95% CI = 95% Confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Following are the simulation expectations for pain score at fixed dose period at 1800, 2400 and 3600 mg using the parameters listed above:



Postherpetic neuralgia

Another population analysis was performed to describe the exposure-response relationship of gabapentin following multiple doses in patients in the two pivotal postherpetic neuralgia clinical studies (945-211 and –295). In these studies, the initial gabapentin treatment was 300 to 900 mg/day with titration over 3 to 4 weeks to final dose dependent upon the study protocol. Following titration, the dose was kept constant for the duration of the study. The overall steady state dose range investigated was 1800 to 3600 mg/day. In addition, data from postherpetic neuralgia patients in 945-306 were added at the completion of model building and compared to results obtained for 945-211 and –295.

Following table summarizes the population parameter estimates of the final model of exposure-response relationship of gabapentin in patients with postherpetic neuralgia:

Parameter (Unit)	Estimate (95% CI)[a]
Placebo Effect	
Immediate Placebo Response (pain score units)	0.171 (0.040, 0.301)
Time-Dependent Placebo Response	
Magnitude (pain score units)	0.761 (0.502, 1.020)
Rate Constant (Day^{-1})	0.0413 (0.021, 0.062)
Drug Effect	
Emax (pain score units)	2.24 (1.42, 3.05)
Exposure (daily dose absorbed) causing 50% of Emax (mg/day)	557.3 (257.4, 857.2)

[a] Confidence interval constructed as estimate ± 1.96 × standard error of estimate.

Final Model:

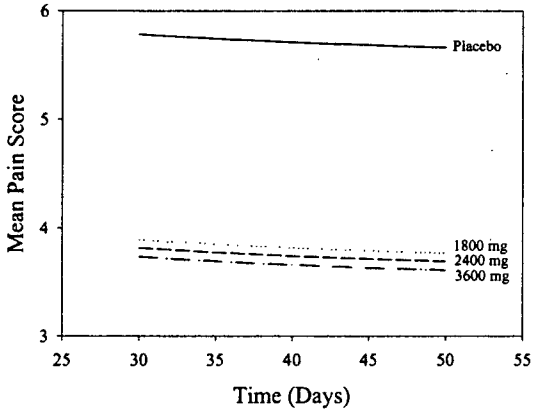
Daily Change from Baseline Pain Score = – (Placebo Effect + Gabapentin Effect)

Baseline = Mean daily pain score during baseline phase.

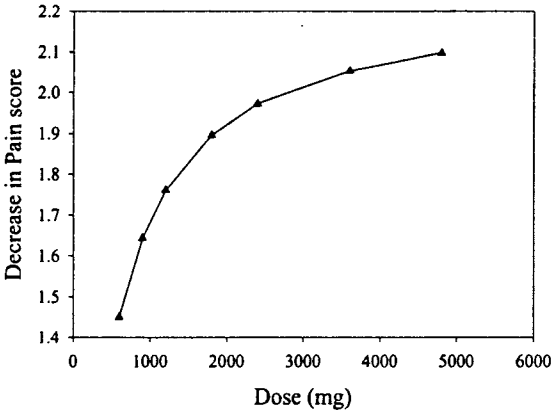
Placebo Effect = (Immediate effect + time dependent effect)

Gabapentin Effect = Emax model with amount absorbed as determinants of exposure.

Following are the simulation expectations for pain score during the fixed dose period at 1800, 2400 and 3600 mg using the parameters listed above:



- Parameter estimates from the final model were used to obtain the following plot which suggest that gabapentin effect increased with dose in a nonlinear fashion.



- Gender had no clinically relevant effect on the exposure-response model.

- Unlike the previous analysis, inclusion of age (modeled as a continuous covariate) did not result in a significant improvement in the fit and was not included in the model. The postherperpetic neuralgia population represents a more homogenous aged population compared to all patients previously tested in five clinical studies.

What is the degree of linearity or nonlinearity in the dose-concentration relationship?

The relationship between gabapentin dose and plasma gabapentin concentrations was assessed during a nonblind, 4-way crossover, rising multiple-dose, dose-proportionality study in 14 healthy subjects. The following 4 treatments were administered sequentially at 1-week intervals: 1 × 400-mg gabapentin capsule q8h for 7 doses; 2 × 400-mg

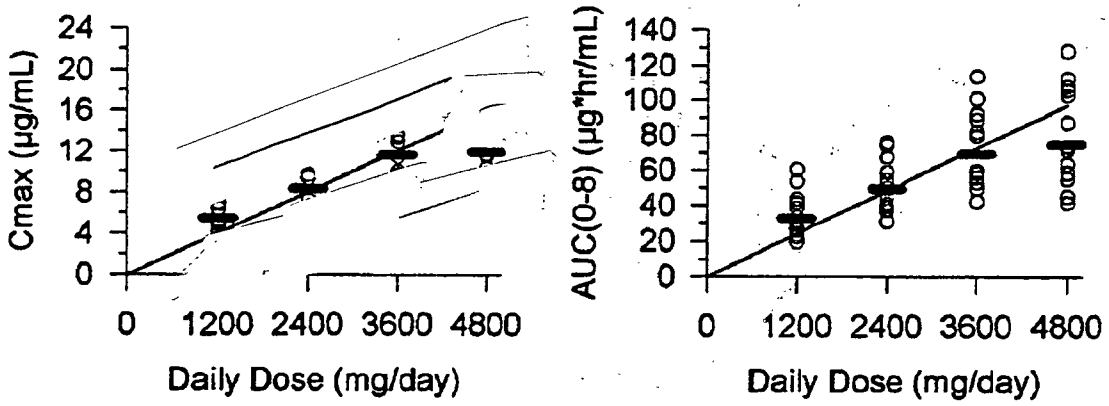
gabapentin capsules q8h for 7 doses; 3 × 400-mg gabapentin capsules q8h for 7 doses; and 4 × 400-mg gabapentin capsules q8h for 7 doses.

Following table summarizes relationships between plasma gabapentin concentration and dose:

Dose (mg/day)	Mean		
	Cmax (µg/mL)	AUC(0-8) µg·hr/mL)	Ae%
1200	5.43	32.8	47.2
2400	8.37	49.7	34.4
3600	11.6	69.5	32.5
4800	11.9	75.1	26.8

Cmax = Maximum steady-state plasma concentration.
AUC(0-8) = Area under the steady-state plasma drug concentration-time curve from 0 time until 8 hours after administration.
Ae% = Percent of dose eliminated as unchanged drug in urine.

Following figure shows the relationship between gabapentin dose and C_{max} and AUC(0-8) values in healthy subjects:



- C_{min} values indicated that steady-state was reached within 24 to 48 hours of initiation of repeated drug administration.

- Mean t_{max} values were similar among treatment groups and averaged 1.6 to 2.3 hours.

- Mean plasma C_{max} and AUC(0-8) values increased with increasing dose. However, the increase was less than proportional to dose.

- Mean Ae% values decreased with increasing dose. Since gabapentin is not appreciably metabolized, the reduction in Ae% is likely the result of a decrease in bioavailability with increasing dose. Gabapentin absorption occurs, at least in part, through the hydrophobic branched chain amino acid transporter, System L, which is saturable at high substrate concentrations. Absolute bioavailability of gabapentin was as the percent of dose excreted in urine. Based on urinary excretion data, the absolute bioavailability of gabapentin following 1200, 2400, 3600, and 4800 mg/day given in divided doses q8h, averaged 47%, 34%, 33%, and 27%, respectively.

4.3 Intrinsic Factors

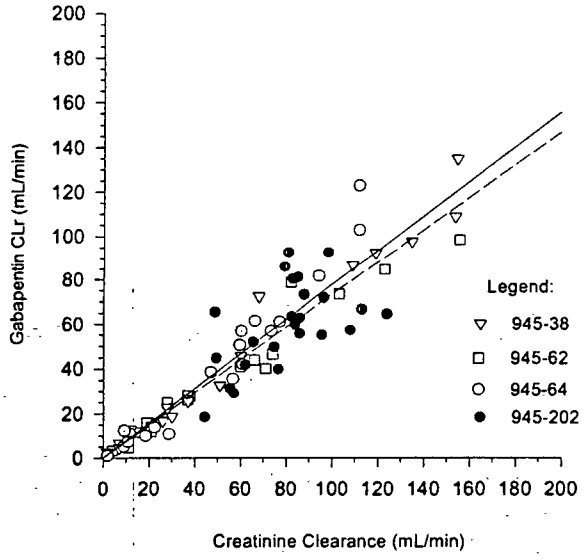
What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Do mass balance studies suggest that renal or hepatic elimination is significant?

Gabapentin was eliminated from the systemic circulation by renal excretion of unchanged drug. Gabapentin is not appreciably metabolized in humans. Because gabapentin is cleared primarily by the kidney, renal impairment is likely to increase the exposure to this drug. Following intravenous administration, gabapentin plasma and renal clearances were approximately equal to creatinine clearance.

Renal Insufficiency

A meta-analysis of data from 14 single-dose studies was conducted to determine gabapentin dosage recommendations for patients with renal impairment. The goal was to provide dosing recommendations that would result in steady-state plasma concentrations in patients with renal impairment that would be similar to concentrations achieved in healthy subjects with normal renal function. In these studies, healthy subjects received single gabapentin doses ranging from 100 to 1600 mg. As shown in the figure below, in various studies gabapentin clearance is directly proportional to CLcr.



Thus, the amount needed to be absorbed in patients with renal impairment ($Abs_{renal\ impairment}$) could be calculated relative to that needed in normal subjects (Abs_{normal}) as:

$$Abs_{renal\ impairment} = Abs_{normal} \cdot \frac{Clcr_{renal\ impairment}}{Clcr_{normal}}$$

where $CLcr_{renal\ impairment}$ and $CLcr_{normal}$ are the CLcr values for patients with renal impairment and normal subjects (120 mL/min), respectively.

The bioavailability of gabapentin is dose-dependent. Therefore, to estimate doses for patients with renal impairment, the relationship between the amount of gabapentin absorbed (as estimated by amount excreted in urine) and gabapentin dose was established. Using this relationship, recommended doses for patients with varying degrees of renal impairment were obtained. According to the sponsor, this will ensure that steady-state plasma gabapentin concentrations in patients with compromised renal function were either equal to steady-state concentrations achieved in patients with normal renal function or not more than twice these concentrations. Following table lists the gabapentin dosages recommended by the sponsor based on renal function:

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose (mg/day)				
≥60	900[a]	1200[a]	1800[a]	2400[a]	3600[a]
≥30-59	400[b]	600[b]	800[b]	1000[b]	1400[b]
>15-29	200[c]	300[c]	400[c]	500[c]	700[c]
15[d]	100[c]	125[c]	150[c]	200[c]	300[c]
	Post-hemodialysis Dose (mg)[e]				
Hemodialysis	125[e]	150[e]	200[e]	250[e]	350[e]

[a] Total daily dose (mg/day) should be divided by 3 and administered 3 times daily (TID).
[b] Total daily dose (mg/day) should be divided by 2 and administered twice daily (BID).
[c] Total daily dose (mg/day) should be administered once daily (QD).
[d] For patients with creatinine clearance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).
[e] Patients on hemodialysis should receive maintenance doses as indicated in the upper portion of the table and an additional post-hemodialysis dose administered after each 4 hours of hemodialysis.

Hemodialysis

In a study in anuric subjects (n = 11) the apparent elimination half-life of gabapentin on non-dialysis days was about 132 hours and during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours.

Hepatic Impairment

Because gabapentin is not metabolized, the sponsor did not conduct any study in patients with hepatic impairment.

Age

The effect of age was studied in subjects 20- 80 years of age. Apparent oral clearance (CL/ F) of gabapentin decreased as age increased, from about 225 mL/ min in those under 30 years of age to about 125 mL/ min in those over 70 years of age. Renal clearance

(CLr) and CLr adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function.

4.4 Extrinsic Factors

What extrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Is there an in vitro basis to suspect in vivo drug-drug interactions?

The ability of gabapentin at 6.84, 34.2, and 171 µg/mL (40, 200, and 1000 µM, respectively) to inhibit cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) was investigated using . Of the 7 human cytochrome P450 isoforms examined, a slight degree of inhibition (14%-30%) was observed only towards CYP2A6 at the highest concentration tested (171 µg/mL = 1 mM). A metabolically-based interaction between gabapentin and a drug whose clearance is dependent upon the major cytochrome P450 enzymes is highly unlikely at plasma concentrations associated with doses up to 3600 mg/day (C_{max} 11.6 µg/mL), the highest recommended daily dose.

Drug-drug interaction studies with naproxen sodium and hydrocodone were conducted as part of development programs for gabapentin/analgesic combination products that

Naproxen: Coadministration (N=18) of naproxen sodium capsules (250 mg) with gabapentin (125 mg) appeared to increase the amount of gabapentin absorbed resulting in 14%, 12%, and 15% higher mean gabapentin C_{max}, AUC(0-8), and Ae% values, respectively. Gabapentin has no effect on naproxen pharmacokinetic parameters. Following table summarizes the effect of naproxen on gabapentin pharmacokinetic parameters:

Parameter	Least-Squares Mean Values		Ratio	90% CI
	Gabapentin Alone (Reference)	With Naproxen (Test)		
N	18	18		
Cmax, µg/mL	1.29	1.47	114	99.7-130
tmax, hr	2.94	2.57	87.4	65.3-110
AUC(0-tlqc), µg·hr/mL	10.7	12.2	113	104-124
AUC(0-∞), µg·hr/mL	11.2	12.5	112	103-122
t½, hr	5.76	5.03	87.4	75.7-99.1
Ae%	62.8	72.5	115	108-123
CLr, mL/min	116	121	105	99.6-110

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% CI = 90% Confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.
N = Number of subjects.
Cmax = Maximum observed plasma drug concentration.
tmax = Time of maximum observed plasma drug concentration.
AUC(0-tlqc) = Area under the plasma drug concentration-time curve from zero time until the time of the last quantifiable concentration.
AUC(0-∞) = Area under the plasma drug concentration-time curve from zero time extrapolated to infinite time.
t½ = Apparent terminal half-life.
Ae% = Percent of dose eliminated as unchanged drug in urine.
CLr = Renal clearance.

Following table summarizes the effect of gabapentin on naproxen pharmacokinetic parameters:

Parameter	Least-Squares Mean Values		Ratio	90% CI
	Naproxen Alone (Reference)	With Gabapentin (Test)		
N	18	18		
Cmax, µg/mL	30.7	30.9	101	92.2-110
tmax, hr	1.20	1.23	102	55.5-149
AUC(0-∞), µg·hr/mL	463	454	98.1	94.7-102
t½, hr	17.5	18.8	107	97.7-117

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% CI = 90% Confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.
N = Number of subjects.
Cmax = Maximum observed plasma drug concentration.
tmax = Time of maximum observed plasma drug concentration.
AUC(0-∞) = Area under the plasma drug concentration-time curve from zero time extrapolated to infinite time.
t½ = Apparent terminal half-life.

Hydrocodone: Coadministration of gabapentin (125 to 500 mg; N=48) decreases hydrocodone (10 mg; N=50) C_{max} and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; C_{max} and AUC values are 3% to 4% lower, respectively, after administration of 125 mg gabapentin and 21% to 22% lower, respectively, after administration of 500 mg gabapentin. Mean hydrocodone pharmacokinetic parameters are presented in the table below:

Parameter	Least-Squares Mean Values		Ratio	90% CI
	Hydrocodone Alone (Reference)	With Gabapentin (Test)		
Cmax, µg/mL				
Test = 125 mg gabapentin	16.0	15.5	97.1	85.1-111
Test = 250 mg gabapentin	16.0	14.1	88.4	78.8-99.1
Test = 500 mg gabapentin	16.0	12.5	78.3	68.7-89.3
AUC(0-∞), µg·hr/mL				
Test = 125 mg gabapentin	124	119	96.4	84.2-110
Test = 250 mg gabapentin	124	104	84.3	74.9-94.9
Test = 500 mg gabapentin	124	97.2	78.7	68.7-90.2

Note: 47 patients received 10 mg hydrocodone without gabapentin; 20 patients received 125 mg gabapentin/10 mg hydrocodone; 30 patients received 250 mg gabapentin/10 mg hydrocodone; and 20 patients received 500 mg gabapentin/10 mg hydrocodone.
Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% CI = 90% Confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.
Cmax = Maximum observed plasma drug concentration.
AUC(0-∞) = Area under the plasma drug concentration-time curve from zero time extrapolated to infinite time.

Hydrocodone increases gabapentin AUC values by 14%, which is not expected to be of clinical significance.

Morphine: A literature article reported increase in mean gabapentin C_{max}, AUC and Ae% values by 24%, 44%, and 26%, respectively, when a 60-mg controlled release morphine capsule was administered 2 hours prior to a 600-mg gabapentin capsule (N=12). The authors suggested that changes in gabapentin pharmacokinetics might have been caused by morphine-induced reduction in gastrointestinal motility, resulting in increased time for gabapentin absorption. Following table summarizes the effect of morphine on the pharmacokinetics of gabapentin:

Parameter	Arithmetic Mean (CV) Values				Ratio
	Gabapentin Alone (Reference)		With Morphine (Test)		
N	12		12		
Cmax, µg/mL	3.7	(13.5)	4.6	(34.8)	124
AUC(0-∞), µg·hr/mL	43.9	(12.1)	63.4	(25.6)	144
t½, hr	8.4	(28.6)	9.1	(84.6)	108
CL/F, mL/min	231	(12.7)	179	(54.7)	77.5
CLr, mL/min	86.9	(23.7)	73.0	(33.2)	84.0
Ae%	37.7	(22.5)	47.4	(39.0)	126

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
CV = Coefficient of variation.
N = Number of subjects.
Cmax = Maximum observed plasma drug concentration.
AUC(0-∞) = Area under the plasma drug concentration-time curve from zero time extrapolated to infinite time.
t½ = Apparent terminal half-life.
CL/F = Total oral clearance.
CLr = Renal clearance.
Ae% = Percent of dose eliminated as unchanged drug in urine.

Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. Following table summarizes the effect of gabapentin on the pharmacokinetics of morphine:

Parameter	Arithmetic Mean (CV) Values				Ratio
	Morphine Alone (Reference)		With Gabapentin (Test)		
N	12		12		
Cmax, µg/mL	57.0	(30.2)	58.5	(30.8)	103
AUC(0-∞), µg·hr/mL	399	(22.5)	423	(19.7)	106
CL/F, mL/min	6924	(22.2)	6472	(21.2)	93.5
CLr, mL/min	86.2	(20.6)	77.4	(22.0)	89.8
Ae%	1.30	(27.7)	1.25	(32.8)	96.2

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
CV = Coefficient of variation.
N = Number of subjects.
Cmax = Maximum observed plasma drug concentration.
AUC(0-∞) = Area under the plasma drug concentration-time curve from zero time extrapolated to infinite time.
CL/F = Total oral clearance.
CLr = Renal clearance.
Ae% = Percent of dose eliminated as unchanged drug in urine.

4.5 General Biopharmaceutics

The gabapentin formulations currently marketed in the United States are 100-mg capsules, 300-mg capsules, 400-mg capsules, 600-mg tablets, 800-mg tablets, and a 50-mg/mL oral solution. Bioavailability/bioequivalence studies associated with the marketed formulations of gabapentin (Neurontin) have been reviewed earlier. All of the marketed gabapentin (Neurontin) formulations have either directly or indirectly been shown to be bioequivalent to a gabapentin solution. Thus all of the marketed formulations are bioequivalent to each other..

4.6 Analytical

Gabapentin concentrations in biological samples were determined using validated The details of assay methods employed in each study are summarized in the following table:

5 Labeling

Following changes are recommended in the "Drug Interactions" section.

Drug Interactions

In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 µg/mL; 1 mM) was a slight degree of inhibition (14%-30%) at gabapentin concentrations up to 171 µg/mL (approximately 15 times the Cmax at 3600 mg/day).

Naproxen:

Hydrocodone: Coadministration of [redacted] (125 to 500 mg; N=48) decreases hydrocodone (10 mg; N=50) Cmax and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; Cmax and AUC values are 3% to 4% lower, respectively, after administration of 125 mg [redacted] and 21% to 22% lower, respectively, after administration of 500 mg [redacted] The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%, [redacted]

Morphine: A literature article reported that when a 60-mg controlled release morphine capsule was administered 2 hours prior to a 600-mg gabapentin capsule (N=12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine.

DOSAGE AND ADMINISTRATION

[redacted]

6 Appendix

6.1 proposed labeling

See attached.

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/s/

Suresh Doddapaneni
5/6/02 01:00:30 PM
BIOPHARMACEUTICS

primary Reviewer Sandip Roy could not sign off in DFS /CPB briefing held on 5/1/02/He Sun did the pharmacometrics review

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Addendum to the primary review

May 11, 2002

NDA: 21-397	Submission Date(s): August 7, 2001
Brand Name	Neurontin
Generic Name	Gabapentin
Pharmacometrician	He Sun, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCPB Division	DPE2
OND division	Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170
Sponsor	Pfizer, Ann Arbor, Michigan
Submission Type; Code	6S
Formulation; Strength(s)	Capsules: 100, 300,& 400 mg Tablets: 600 & 800 mg
Oral Solutions:	250 mg/5 mL
Indication	Management of [redacted] postherpetic neuralgia

1 Executive Summary

Population pharmacokinetics and pharmacodynamics (PK/PD) analyses were conducted to establish a linkage across two pivotal clinical trials, trial 211 and 430, that used two different final treatment doses. Two kinds of new data analyses were performed and summarized in this addendum: a summary statistics to compare the observed clinical pain score at various dose levels or days after starting the therapy, and modeling and simulation analyses to check the agreements across different trials.

Summary statistics indicate that the pain relief scores for two pivotal clinical trials, trial 211 (with 3600-mg final dose) and trial 430 (with 2400-mg final dose) at various dose levels/days of therapy were in good agreement.

By taking patient demographic variables, baseline pain, dose and placebo effects into consideration, modeling and simulation analyses indicate that pain scores for trial 211 or 430 can be predicted with confidence based on information from either the four other trials with various pain types, or from the comparative pivotal trial. These results suggest that the two pivotal clinical trials would be the same in pain relief outcomes if the final doses were the same (i.e. these two trials are cross-confirming).

In addition, modeling and simulation analysis results suggest that pain relief profile across the three different types of pains may also be cross-predictive.

2 Recommendation

From OCPB view point, it appears that trial 430 (that used the 2400-mg final dose) and trial 211 (that used the 3600-mg final dose) were in good agreement with each other and cross-confirming with respect to the pain relief profiles. Furthermore, it appears that if trial 430 were to have been continued on to a final dose of 3600-mg, the pain relief profile would have been similar to that obtained in trial 211.

Overall, a new clinical trial replicating the doses may not be needed.

Also, it appears that additional benefit is not apparent at doses higher than 2400-mg.

He Sun, Ph.D.
Pharmacometrician, OCPB/DPEII

Suresh Doddapaneni, Ph.D.,
Team Leader

P.S. The addendum materials have been presented and discussed in a review group meeting with Medical, Statistical and Clinical Pharmacology Division Managers and review team members on May 9, 2002 at 10:00am.

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3 Summary of Data Analyses

3.1 Background information

Additional population pharmacokinetics and pharmacodynamics (PK/PD) analyses were conducted to establish a linkage across two pivotal clinical trials, trial 211 and 430, that used two different final treatment doses. Data from five clinical trials with 60,462 observations from 1338 subjects were available for this analysis. In these clinical trials, the initial gabapentin treatment was 300 to 900 mg/day with titration over 3 to 4 weeks to a final fixed dose of 1800 to 3600 mg/day for 4 weeks.

In the original review, it was known that increasing age resulted in increased pain relief response to gabapentin. This is possibly related to an age associated decrease in renal function resulting in increased steady state systemic exposure of gabapentin. Gender had no clinically significant effect on the exposure-response relationship. Also, capacity limited absorption kinetics was documented.

3.2 Summary statistics analyses:

The summary statistic analyses indicate that the pain relief scores for the two pivotal clinical trials, trial 211 (with 3600-mg final dose) and trial 430 (with 2400-mg final dose) at various dose levels/days of therapy were in good agreement. Pain relief score from other three non-pivotal trials in different patient populations were little higher or lower than those observed from the two pivotal trials.

Calculation functions used:

Pain score = observed pain score at a given dose level/time
Baseline = mean of pain score before therapy (from day –7 to day 0).
Pain relief score = pain score – baseline
Drug effect = Pain relief due to drug – Pain relief from placebo.
n = number of observations at a given dose or time point

The observed pain scores from placebo and drug therapy groups at various time-points are displayed in the following figures. Large intersubject variabilities were observed and not explainable by known subject demographic variables (age, body weight, height, gender, and race).

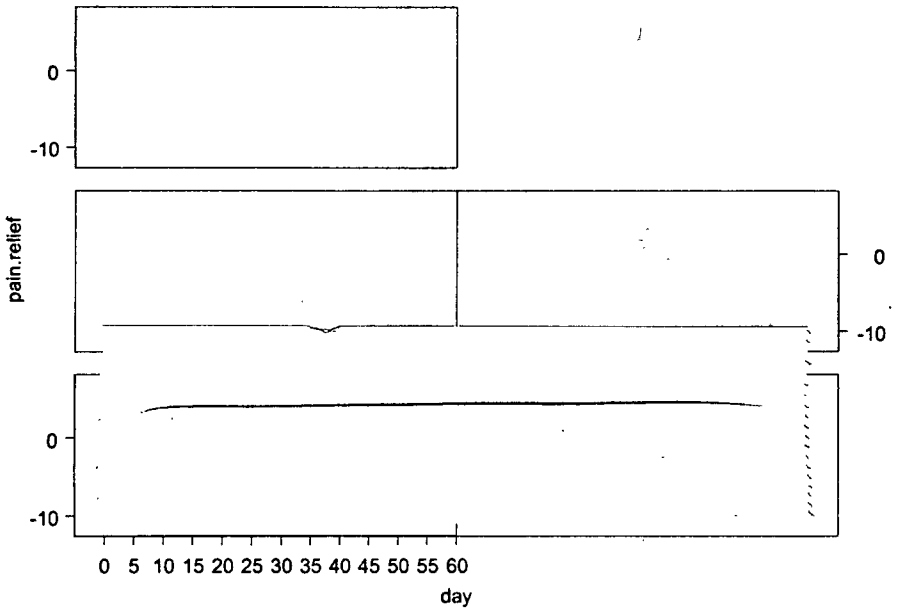

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Figure 1 and 2. Pain relief from drug treatment and placebo groups. All raw observations from all five trials are displayed. A large intersubject variability is seen. Pain relief gradually approaches steady-state over a 30 to 50 days of time which is contributed from the titration process.

Mean (SD) values of pain score, pain relief score, as well as the associated number of observations were calculated for each dose levels for all trials. The mean pain scores and mean pain relief scores then were plotted against the associated dose for all trials with n>=150 (Figure 3 and 4) to examine the dose-response relationship. It was observed that trial 211 and 430 show similar dose-response profiles either using all data or data with n=>150 (figures 5)

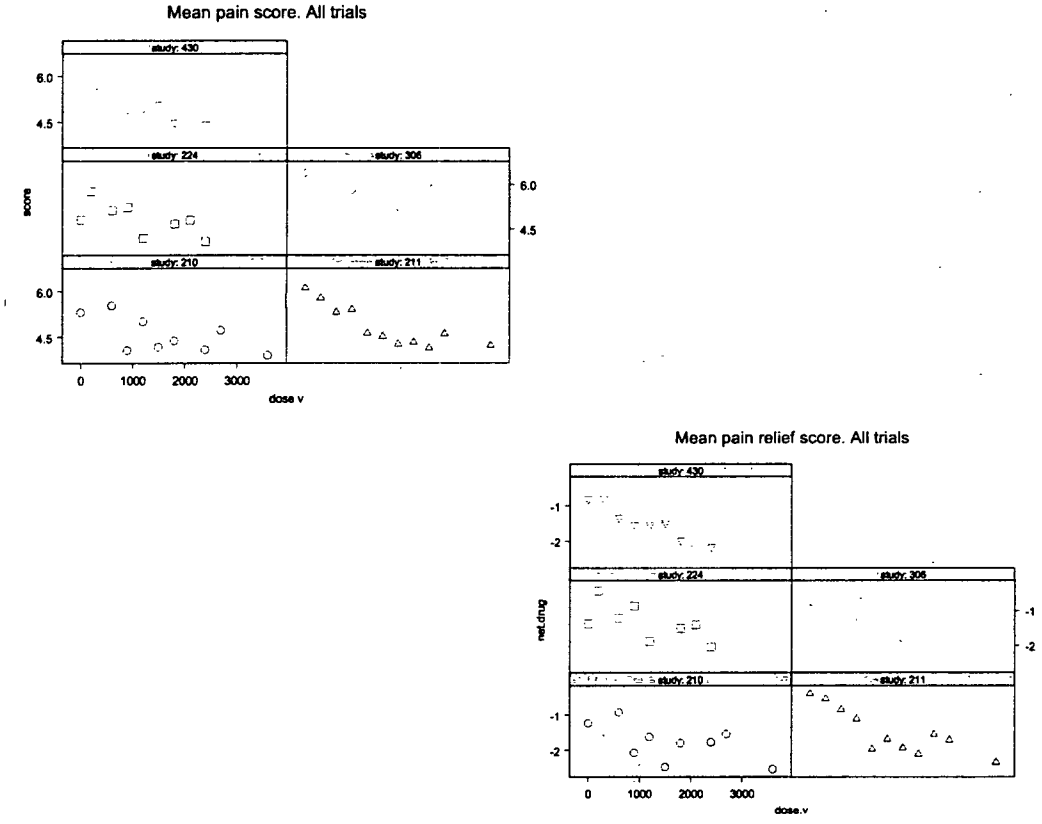


Figure 3 and 4. Pain score and pain relief score from drug treatment group. Observations with n >=150 from all 5 trials are displayed. Trial 211 and 430 show similar dose-response profile while other 3 trials for different types of pains and titration protocols exhibited various profiles. Please note that 2400-mg dose was the final dose in trial 430 and 3600-mg dose was the final dose in trial 211.

Overall, it appears that the pain scores and pain relief scores of trial 211 and trial 430 are similar. However, this type of analysis did not take titration time/protocol, pain type, placebo effect, baseline value and patient population into consideration and drug bioavailability and systemic exposure factors were not corrected. Therefore, in-depth modeling analyses were further conducted.

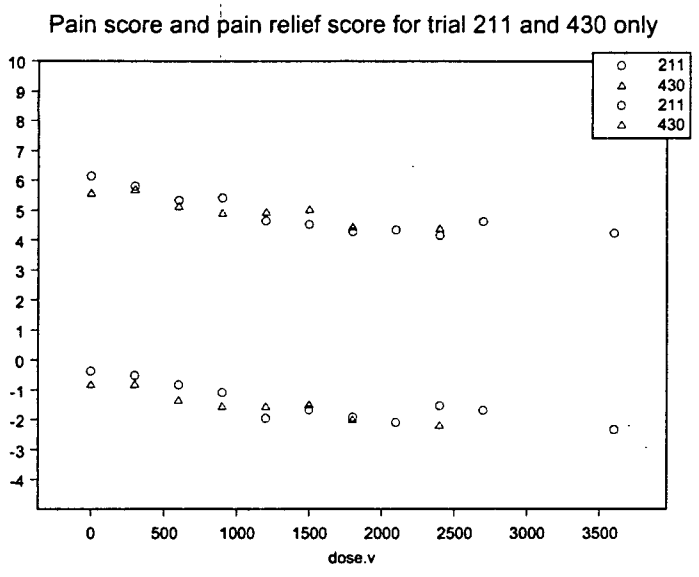


Figure 5. Pain score from trial 211 and 430. Observations with n >=150 are displayed. Trial 211 and 430 show very similar dose-response profile. Please note that 2400-mg dose was the final dose in trial 430 and 3600-mg dose was the final dose in trial 211.

3.3 Modeling and Simulation Analyses

3.3.1 Section Summary

To more precisely link the two pivotal trials by accounting for the effects of dose, age, baseline, treatment and placebo etc. on pain relief, modeling and simulation analyses was performed. Results indicate that pain scores from trial 211 or 430 can be adequately predicted based on information from either the four other trials, or from the comparative pivotal trial, suggesting that the two pivotal clinical trials are the same in pain relief scores would the final doses were to be the same.

In addition, analysis results suggest that pain relief profile across the three different types of pains may also be cross-predictive.

3.3.2 The concept of the analyses

The key challenge of these analyses is to determine if the two pivotal trials, trial 211 and trial 430 that used different dose levels, are cross-confirming. If a set of PK/PD model parameters obtained based on data excluding a trial (e.g. trial 211) can predict pain score of the trial (trial 211) adequately, then the trial (trial 211) must be the same as all other trials.

The by-product of the analyses is that, if all trials can be simultaneously fitted well with a sets of shared dose-response parameters with only one parameter to be specific for pain type adjustment, then a prediction of pain score from one study to the other may be made and referenced for future trial designs.

3.3.3 Methods:

Nonlinear mixed-effect modeling analyses were conducted. Individual observed pain scores were the dependent variable and was modeled as a function of:

Pain score = Baseline scores – Pain relief from placebo – Pain relief from drug – Pain relief following titration time course.

Where

Baseline = the mean pain scores from day –7 to day 0
Pain relief from placebo = the pain score of the parallel placebo arm of the trial, which is also a function of treatment length and pain type.
Pain relief from drug = modeled using the known applicable Emax model. In the model, the exposure was corrected for dose-dependent bioavailability, the effect of aging on systemic exposure, and the dose.
Pain relief following titration time = modeled as an exponential decline over time.

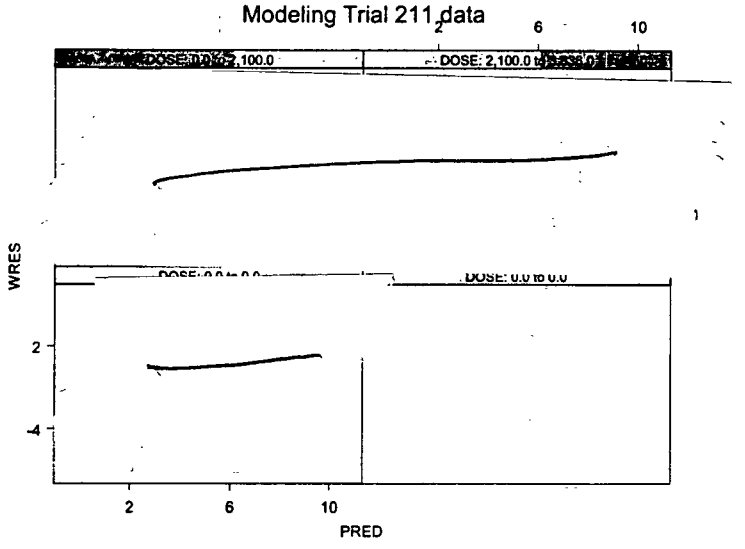
Pain score data were fitted with the above function using NONMEM on

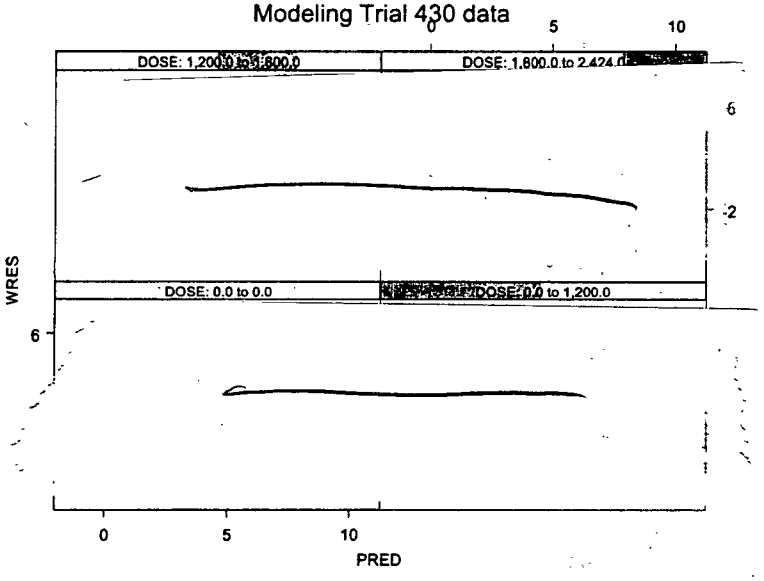
With the estimated model parameters, pain scores of the trial that was not included in the modeling process were predicted via simulations (attachment 2 for S-plus code).

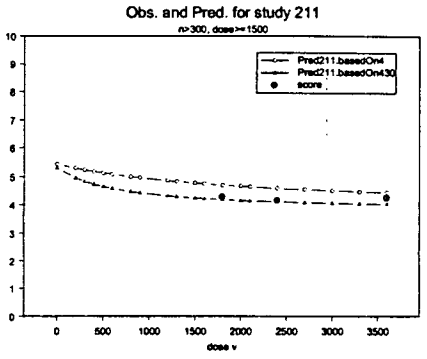
3.3.4 Results

The NONMEM modeling outputs were given at the attachment section. These outputs represent simultaneous modeling four-trials, or one trial at a time. Goodness-of-fit examples are provided in figure 6-7. Prediction of pain score for trial 211 is shown in Figure 8 and 9. The predictions were made based parameters from modeling all the other four trails or modeling trial 430 only. Prediction of pain score for trial 430 is shown in Figure 9 and 10. The predictions were made based parameters from modeling all the other four trails or modeling trial 211 only.

Figure 6 and 7. Goodness-of-fit examples







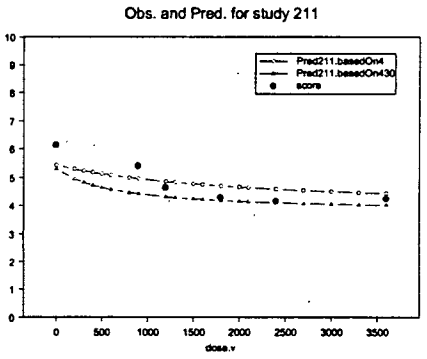
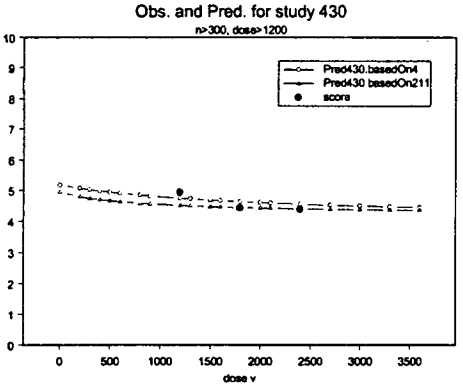


Figure 8 and 9. Observed and predicted pain score at all dose levels and at higher dose levels with n>=300 for trial 211. Predictions were made based on either all four other trials or the comparative trial 430 only. An excellent match between predicted and observed pain score at 3600-mg is seen.



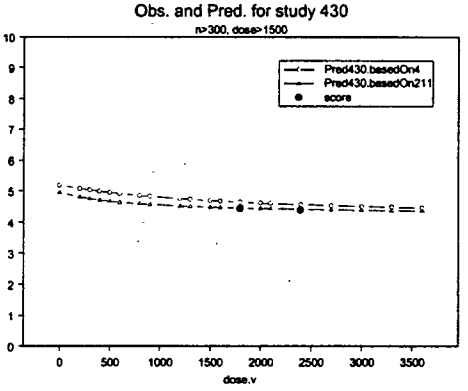


Figure 10 and 11. Observed and predicted pain score at higher dose levels with n>=300 for trial 430. Predictions were made based on either all four other trials or the comparative trial 211 only. An excellent match between predicted and observed pain scores at 2400-mg dose is seen.

The model explains data adequately under either simultaneous fitting or individual fitting conditions.

The predicted pain score values based on other trials at various doses level for both trial 211 and 430 are in excellent agreement with the actual observed values.

The projected pain score at 3600-mg for trial 430 is same as those observed from trial 211. The estimated pain score at 2400-mg for trial 211 is same as those observed from trial 430. Therefore, the two trials are cross-confirming.

3.3.5 Conclusion:

Pain relief score in Trial 211 and 430 are nearly identical should the dose were to be the same. The two trials are cross-confirming.

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/s/

He Sun
5/13/02 10:22:27 AM
PHARMACOLOGIST
This is an addendum to the original CPB review of May 2. Suresh, as we discussed this morning. Thanks for the opportunity to work on the excellent project with you !

Suresh Doddapaneni
5/13/02 01:08:24 PM
BIOPHARMACEUTICS

M Sunzel

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission date: January 15, 2002

Brand Name	Neurontin®
Generic Name	gabapentin
Reviewer	Maria Sunzel, Ph.D.
Team Leader	Ramana Uppoor, Ph.D.
OCPB Division	Pharmaceutical Evaluation I (DPE1, HFD-860)
OND Division	Neuropharmacological Drug Products (HFD-120)
Sponsor	Pfizer Inc., 2800 Plymouth Road, Ann Arbor, MI
Relevant IND	Not applicable
Submission Type; Code	Labeling supplement
Formulation; Strengths	Capsules (100, 300 & 400 mg), tablets (600 & 800 mg), oral solution (250 mg/5 mL syrup)
Indication	

1 SUMMARY AND CONCLUSIONS

This review concerns revisions to the label for Neurontin® (gabapentin capsules, tablets, & oral solution), that currently is approved as adjunctive therapy in patients with partial epilepsy. The primary clinical pharmacology review was conducted by Dr S. Roy (HFD-870), as the sponsor has submitted data for a new indication, the management of [redacted] post-herpetic neuralgia (NDA 21-397), to the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170). The sponsor has revised the label and includes new text for the CLINICAL PHARMACOLOGY, PRECAUTIONS: Drug interactions, DOSAGE AND ADMINISTRATION sections, but the main revisions are with regard to efficacy and safety (See Appendix for sponsor's new label proposal). Since the new NDA is reviewed within DPE2 of the Office of Clinical Pharmacology & Biopharmaceutics (OCPB), the label text has been discussed within OCPB (representatives from DPE1 & DPE2). This reviewer finds Dr. Roy's label revisions adequate. However, additional comments from DPE1 have also been put forward to the DPE2 review team.

The proposed maximum daily dose of 3600 mg/day for management of [redacted] post-herpetic neuralgia is higher than the maximum dose recommended for epilepsy (1800 mg/day) in the current labeling. The sponsor conducted a clinical pharmacology study to assess the dose-proportionality of steady-state plasma gabapentin concentrations in healthy adult subjects at doses up to 4800 mg/day (1200, 2400, 3600 & 4800 mg/day given in 3 divided doses; 4-way cross-over study, n=14). The gabapentin dose-proportionality study currently described in the label is based on data from 4 subjects per dose level.

The comments on the label by DPE 2 can be found on page 4, Appendix, and the sponsor's proposed, entire label is attached in the Appendix (page 5-30).

2 LABEL CHANGES AND COMMENTS

In summary, the sponsor proposes the following changes to the Neurontin label (capsules, tablets & oral solution) with regard to the sections that are reviewed by OCPB:

M Sunzel

3 RECOMMENDATION

The Division of Pharmaceutical Evaluation I (DPE1), Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the evaluation of the label revision of Neurontin acceptable if the PK studies are considered adequate by DPE2. Additional, minor comments have been conveyed to the review team in DPE2 regarding NDA 21-397. Please convey the label comments to the HFD-170 team.

4 SIGNATURES

Maria Sunzel, Ph.D. _____

RD/FT initialed by Ramana Uppoor, Ph.D. _____

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

c.c.: NDA 20-235/SE8-023, NDA 20-882/SE8-009, NDA 21-129/SE8-010, HFD-120 (Ware, Mani, Feeney), HFD-860 (Mehta, Marroum, Uppoor, Sunzel), HFD-870 (Doddapaneni)

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M Sunzel

5 APPENDIX (Labeling)

5.1 The Agency's revisions to the sponsor's label

Text extracted from Dr S Roy's review (DPE2) of NDA 21-397, dated 05/06/02.

Labeling

Following changes are recommended in the "Drug Interactions" section.

Drug Interactions

***In vitro* studies were conducted to investigate the** potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 µg/mL; 1 mM) was a slight degree of inhibition (14%-30%) No inhibition was observed with any of the other isoforms tested at gabapentin concentrations up to 171 µg/mL (approximately 15 times the Cmax at 3600 mg/day).

Naproxen: Coadministration (N=18) of naproxen sodium capsules (250 mg) with (125 mg) appears to increase the amount of gabapentin absorbed by 12% to 15%. Gabapentin has no effect on naproxen pharmacokinetic parameters.

Hydrocodone: Coadministration of (125 to 500 mg; N=48) decreases hydrocodone (10 mg; N=50) Cmax and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; Cmax and AUC values are 3% to 4% lower, respectively, after administration of 125 mg and 21% to 22% lower, respectively, after administration of 500 mg The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%.

Morphine: A literature article reported that when a 60-mg controlled release morphine capsule was administered 2 hours prior to a 600-mg capsule (N=12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine.

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/s/

Maria Sunzel
5/13/02 07:32:44 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
5/14/02 10:03:08 AM
BIOPHARMACEUTICS

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