CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022544Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 022544	Submission Date: 03/30/2010
Relevant IND(s):	71439
Submission Type; Code:	505 (b) (2)
Reference Drug:	Neurontin®
Brand Name:	Gralise
Generic Name:	Gabapentin
Formulation; Strength(s):	Extended-release tablets, 300 and 600 mg
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
Pharmacometrics Reviewer:	Atul Bhattaram, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Anesthesia and Analgesia Products
Sponsor:	Abbott
Proposed Indication:	Management of post-herpetic neuralgia
Proposed Dosage Regimen:	Once daily dosing with evening meal with the following titration schedule

	Day 1	Day 2	Day 3-6	Day 7-10	Day 11-14	Day 15
Daily dose (mg)	300	600	900	1200	1500	1800

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1.0 Executive Summary

1.1 Recommendation

This submission is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement is reached between Agency and Sponsor regarding the labeling language.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

Abbott submitted NDA 022544, gabapentin extended release tablets (G-ER) for the management of post-herpetic neuralgia (PHN) in adults under section 505 (b) (2) of the Federal Food Drug and Cosmetic Act. The referenced drug is gabapentin immediate-release (IR) formulation, Neurontin® (NDAs 20-129, 20-235, 20-882, 21-397, 21-423, 21-424).

Gabapentin immediate release formulation (Neurontin®) was originally approved in December, 1993 (NDA 20-235) as adjunctive therapy in the treatment of partial seizures. It was subsequently approved for the management of PHN in adults (May 2002, NDA 21-424). The approved dose of Neurontin® in adults with PHN is 1800 mg/day, administered in 3 divided doses. There was no significant increase in efficacy, although doses upto 3600 mg/day of Neurontin® were tested in clinical trial(s). The most common adverse reactions reported for gabapentin in PHN patients (Neurontin® label) were dizziness, somnolence and peripheral edema, which occurred at a frequency of 28%, 21%, and 8%, respectively.

The proposed gabapentin formulation is an extended release, gastro-retentive formulation (G-ER). The proposed mechanism for extended release characteristics of G-ER is that when administered with a meal, the G-ER tablet swells to a size that promotes gastric retention for several hours in the fed state. During this time, drug is gradually released over ~ 8-10 hr period for absorption in the intestine. Glumetza (metformin HCI ER Tabs) and Proquin XR (ciprofloxacin HCl) previously approved by the Agency contain similar gastro-retentive formulations.

G-ER tablets 300 mg and 600 mg are intended for once-daily (QD) administration of 1800 mg with evening meal with the following-titration schedule:

	Day 1	Day 2	Day 3-6	Day 7-10	Day 11-14	Day 15
Daily dose	300 mg	600 mg	900 mg	1200 mg	1500 mg	1800 mg

In support of this NDA, sponsor submitted data from the following clinical pharmacology and clinical studies. As the G-ER is to be taken with meals, all the clinical and clinical pharmacology studies were conducted under fed conditions.

- Clinical Pharmacology Studies include:
    1) Pilot Relative bioavailability (BA) of G-ER versus Neurontin® tablets (studies 81-0008).
    2) Dosage-form proportionality of 2x300 mg G-ER tablets versus 1x600 mg G-ER tablet (Study 81-0040)
    3) Dose-proportionality of G-ER tablets in the range of 600 to 2400 mg administered as multiples of one, two, three, and four 600 mg tablets (Study 81-0044)
    4) Food effect under fasting, low-fat and high fat conditions (Study 81-0048)
    5) Relative bioavailability, single and multiple dosing pharmacokinetics (PK) of G-ER (Study 81-0049)
    6) In-Vitro/In-Vivo correlation PK study (Study 81-0050) (Reviewed by Dr. Sandra Suarez, Biopharmaceutics reviewer of ONDQA).
    7) Modeling and simulation for G-ER dosing in renally impaired patients using gabapentin plasma concentration data from 3 PK studies (Reports 85-0009 and 85-0010).

- Clinical Studies include one phase 2 (Study 81-0038) and two phase 3 (Studies 81-0045 and 81-0062) randomized double blind studies of safety and efficacy of G-ER tablets in treatment of PHN.

Relative bioavailability study 81-0008 was a pilot PK study, conducted with a pilot formulation. Dose-proportionality, dosage-form proportionality, and phase 2 clinical studies were conducted with the phase 2 formulation. The relative bioavailability, single dose, and multiple dose PK study (Study 81-0049), food effect study (study 81-0048), and the two phase 3 clinical studies were conducted with phase 3 formulations. Phase 3 and to-be-marketed formulations are exactly the same except for color and debossing for 600 mg and debossing for 300 mg. Even though 300 mg strength of phase 3 formulation was not evaluated in the PK studies 81-0048 and 81-0049, it was evaluated in the phase 3 studies 81-0045 and 81-0062. The 300 mg strength is meant for use during the titration phase and only the 600 mg strength is used during the maintenance treatment.

The oral BA of IR gabapentin is ~60% at a dose of 900 mg/day. In the absorption of gabapentin from small intestine, an L-amino acid transport system is involved, which is saturable. This saturable transporter is reportedly responsible for less than dose-proportional increase in gabapentin exposure with increasing doses. The bioavailability

of IR gabapentin is 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day. For G-ER also, the bioavailability decreases with increasing doses. The AUC normalized to dose (multiples of 600 mg) decreased from the 600 mg dose (100%) to 89% for 1200 mg, 85% for 1800 mg, and 76% for 2400 mg (study 81-0044).

Gabapentin is eliminated unchanged renally. Gabapentin half-life and systemic clearance values were independent of dose and not altered following repeated administration. Gabapentin half-life is approximately 5 to 7 hr in healthy subjects.

For IR gabapentin, food has only a slight effect on the rate and extent of absorption (14% increase in AUC and C_{max}) and is labeled to be taken with or without food. However for the G-ER formulation, the dosage form functionality depends on administration with food and is labeled to be taken before evening meals. All 6 PK studies, one phase 2 and two phase 3 trails were performed in the fed state. The effect of food (fat) on the PK of G-ER was evaluated in a dedicated food effect study (Study 81-0048) in which G-ER 600 mg was administered after fasting, low fat (30% fat calories) and high fat (50% fat calories) meals. The data show that the AUC and Cmax of G-ER increases with increase in fat content of the meals. The AUC increases by 33 and 118%, respectively after a meal containing 30% and 50% of its calories from fat compared to the fasting conditions. Similarly, Cmax increases by 33, and 84%, respectively with 30% and 50% fat content in meals. Because, G-ER release mechanism is dependent on gastro-retention driven by fed conditions and product was administered under fed conditions in all Clin Pharm and Clinical studies, the observed food (fat) effect on G-ER exposure does not warrant timing of product administration in relation to meal consumption. Sponsor is appropriately proposing that G-ER formulation should be taken with evening meal. By specifying that the product be taken with evening meal (as opposed to generic term food), some of the variability in meal composition likely to be encountered is reduced as evening meals generally tend to be more elaborate than a simple snack. Since taking the G-ER tablets under fasting conditions reduces the exposure, adding the following additional language will make it clear that product is not be taken under fasting, ‘ If G-ER is taken while fasting, the bioavailability will be lower substantially’.

G-ER 1800 mg administered once-daily demonstrated comparable BA to Neurontin®, administered 600 mg three times daily. The G-ER (dosed with the evening meal) has similar AUC and Cmax values as that of IR regimen. The relative BA was evaluated in four different studies (Studies 81-0008, 81-0040, 81-0049, 81-0050). Study 81-0049 was a dedicated relative BA study of G-ER vs Neurontin® after single and multiple dose (5 days) administration, in which G-ER was dosed QD (1800 mg evening dose) or BID (600 mg in the morning, 1200 mg in the evening) versus Neurontin® (600 mg) TID in fed conditions. Results show that BA of G-ER was comparable to Neurontin® as evident by similar values of $AUC_{0\ \infty}$, Cmax after single dose and $AUC_{0\ 24}$, Cmax at steady state between G-ER and IR. The ratios of geometric means and 90% CIs for Cmax and AUC were within 80-125% limits both after single and multiple dose administration. The terminal elimination half life was similar between G-ER (~8.5 h) and IR (8.4 h). After multiple dosing, G-ER showed no accumulation, similar to that of Neurontin®. Steady state was reached after 2 days. The trough concentrations are about 45% lower with G-ER tablets. With respect to % degree of fluctuation and % degree of swing, values for

both these parameters are higher for G-ER compared to Neurontin (141 vs. 102 for % fluctuation and 456 vs. 246 for % swing parameters). It should be noted that G-ER tablet exhibiting the multiple dose pharmacokinetic characteristics as discussed above was evaluated in safety and efficacy trials 81-0045 and 81-0062.

Two 300 mg and one 600 mg G-ER tablets evaluated with phase 2 formulation have equivalent exposure (study 81-0044).

Similar to findings for Neurontin®, there were no clinically significant gender and race-related differences in PK of G-ER that warrant dosage adjustment. Elderly subjects do not require dosage adjustment unless renal function is compromised.

Because gabapentin is cleared primarily by the kidneys, (gabapentin plasma and renal clearances were approximately equal to creatinine clearance) renal impairment is likely to increase the exposure to this drug. In patients with impaired renal function, gabapentin clearance is markedly reduced and dosage adjustment is necessary.
Sponsor did not evaluate the impact of renal impairment on gabapentin pharmacokinetics after administration of G-ER formulation. The effect of decreased renal function on gabapentin pharmacokinetics and dose recommendations was addressed by the sponsor using prior knowledge of effect of renal impairment on gabapentin clearance and a pharmacokinetic model for gabapentin concentrations after administration of G-ER formulation in healthy subjects. These were reviewed by Dr. Bhattaram and he found the simulations conducted by the sponsor acceptable in the patients with creatinine clearance of > 30 mL/min and is not acceptable for the patients with creatinine clearance range of 15-30 mL/min (for additional details see Pharmacometrics review by Dr. Bhattaram, Ph.D. attached as an appendix to this review). As per sponsor, patients with creatinine clearance range 15-30 mL/min would be administered an initial once-daily dose of (b) (4) , which is an higher starting dose compared to once-daily 200 mg Neurontin® immediate release formulation. The higher initial once-daily dose could lead to tolerability issues with G-ER formulation in comparison to Neurontin® immediate release formulation in patients with creatinine clearance between 15 and 30 mL/min. In addition, Neurontin® already has a once daily administration recommendation for this subgroup of creatinine clearance 15-30 mL/min.

Based on the simulations, the proposed dosing of G-ER in renally impaired patients based on creatinine clearance are:

- 1800 mg in patients with creatinine clearance of > 60 mL/min
- 600 to1800 mg in patients with creatinine clearance of 30-60 mL/min.

The starting dose of G-ER must be 300 mg in patients with and without any degree of renal impairment.
In patients with a creatinine clearance of 15-30 mL/min or in patients receiving hemodialysis, G-ER should not be administered.

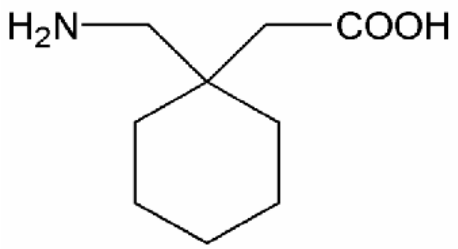
Overall, adequate information has been provided characterizing the clinical pharmacology aspects of gabapentin extended release formulation.

2.0 Question Based Review

2.1 General Attributes of the Drug

2.1.1 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 $C_9H_{17}NO_2$ and a molecular weight of 171.24. The molecular structure of gabapentin is:



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

Drug product

G-ER 300 mg tablets are white to off-white, film-coated, 0.3937" X 0.6299" modified oval shaped tablets that are 714.0 mg in weight, and debossed with "SLV" on one side and with "300" on the other side. The tablet contains 300 mg of gabapentin active. G-ER 600 mg tablets are beige, film-coated, 0.4330" x 0.7450" modified oval shaped tablets that are 1020.0 mg in weight, and debossed with "SLV" on one side and with "600" on the other side. The tablet contains 600 mg of gabapentin active

The excipients of the drug product for 300 mg and 600 mg tablets are similar which include polyethylene oxide, hypromellose, copovidone, magnesium stearate (b) (4) , (b) (4) microcrystalline cellulose, expect for and Opadry® II White for 300 mg and Opadry® II Beige for 600 mg tablets. The quantitative compositions of the G-ER tablets, 300 mg and 600 mg, are described in Table 2.1.1. As can be seen from the tablet, the two strengths are not compositionally proportional.

Table 2.1.1: Quantitative composition of G-ER tablets, 300 and 600 mg.

Component[3]	300 mg		600 mg	
	Quantity (mg/tablet)	w/w [%]	Quantity (mg/tablet)	w/w [%]
Gabapentin	300.00	(b) (4)	600.00	(b) (4)
Polyethylene Oxide	(b) (4)			
Hypromellose				
Microcrystalline Cellulose				
Copovidone				
(b) (4)				
Magnesium Stearate				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
Opadry® II White				
(b) (4)				
Total Coated Tablet	714.00	100.0	1020.0	100.0
(b) (4)				

3. All excipients with the exception of Opadry® II White are tested according to the corresponding monographs in the current editions of the NF/USP/EP.

In clinical and clinical pharmacology studies, the following drug product batches were used for 300 mg and 600 mg strengths.

- Clinical Pharmacology Studies:
  - Study 81-0008 Pilot PK study
    - Pilot formulation GR6 (batch # 010100)
    - Pilot formulation GR8 (batch # 010101 and 010102)
  - Study 81-0040- Dosage-form proportionality /RBA study-
    - Lot #1079 (300 mg) and 1082 (600 mg) - Phase 2 formulations
  - Study 81-0044- Dose-proportionality study
    - Lot #1082 (600 mg)- Phase 2 formulation
  - Study 81-0048- Food effect study
    - Lot #6T4221 (600 mg) - Phase 3 formulation
  - Study 81-0049- Single and multiple dosing PK study
    - Lot #6T4221 (600 mg) - Phase 3 formulation
  - Study 81-0050- IVIVC study
    - (b) (4)

- Clinical Studies:

Phase 2

- Study 81-0038:
  - Lot #1078 (300 mg)- Phase 2 formulation
  - Lot #1080 and 1081 (600 mg)- Phase 2 formulation

Phase 3

- Study 81-0045:
  - Lot #06T419R (300 mg)- Phase 3 formulation
  - Lot #06T422R Lot #06T4222 (600 mg)- Phase 3 formulation
- Study 81-0062:
  - Lot #07T1171R (300 mg)- Phase 3 formulation
  - Lot #07T026R (600 mg)- Phase 3 formulation

2.1.2 What are the proposed mechanism of action and therapeutic indication(s)?

Mechanism of action:

The exact mechanism of action of gabapentin in humans is unclear. However, its therapeutic action on neuropathic pain is thought to involve binding to α2δ calcium channel subunits of voltage gated N-type Ca^{2+} ion channels thereby preventing the entry of Ca^{2+}, leading in turn to reduced neurotransmitter release and attenuation of post-synaptic excitability.

The proposed therapeutic indication for gabapentin is the management of post-herpetic neuralgia in adults ≥18 years of age.

2.1.3 What are the proposed dosage and route of administration?

The proposed G-ER tablets are intended for once-daily (QD) oral administration of 1800 mg with evening meal with the following-titration schedule:

	Day 1	Day 2	Day 3-6	Day 7-10	Day 11-14	Day 15
Daily dose	300 mg	600 mg	900 mg	1200 mg	1500 mg	1800 mg

2.1.4 What is G-ER to-be-marketed formulation?

G-ER is a gastro-retentive drug delivery system. During the drug development, sponsor used Phase 2 and Phase 3 formulations in the clinical and clinical pharmacology studies (see section 2.1.1). The final to be marketed 300 mg G-ER formulation differs from Phase 3 formulation in debossing, whereas 600 mg G-ER differs in debossing and color.

The dose proportionality, dosage form proportionality and phase 2 efficacy studies were conducted with phase 2 formulation. The food effect, relative BA, single dose, multiple dose, phase 3 efficacy studies were conducted with phase 3 formulation.

2.1.5 What are the core studies submitted in this NDA?

The following are the core studies submitted in this NDA.

- Clinical Pharmacology Studies:

1) Relative bioavailability of ER versus Neurontin® tablets (studies 81-0008).
2) Dosage-form proportionality of 2x300 mg G-ER tablets versus 1x600 mg G-ER (Study 81-0040)
3) Dose-proportionality of G-ER administered as multiples of 600 mg in the range of 600 mg to 2400mg (Study 81-0044)
4) Food effect under fasting, low-fat and high fat conditions (Study 81-0048)
5) Multiple dosing PK of G-ER (Study 81-0048)
6) In-Vitro/In-Vivo correlation PK study (Study 81-0050) (Reviewed by Dr. Sandra Suarez, Biopharmaceutics reviewer of ONDQA).
7) Modeling and simulation for G-ER dosing in renally impaired patients using gabapentin plasma concentration data from 3 pharmacokinetic studies (Report 85-0009 and 85-0010).

- Clinical Studies include one phase 2 (Study 81-0038) and two phase 3 [Studies 81-0045 and 81-0062 (pivotal study)] randomized double blind studies of safety and efficacy of G-ER tablets in treatment of PHN.

Relative bioavailability study 81-0008 was a pilot PK study, conducted with a pilot formulation. Dose-proportionality, dosage-form proportionality, and phase 2 clinical studies were conducted with the phase 2 formulation. The relative bioavailability, single dose, and multiple dose PK study (Study 81-0049), food effect study (study 81-0048), and the two phase 3 clinical studies were conducted with phase 3 formulations. Phase 3 and to-be-marketed formulations are exactly the same except for color and debossing for 600 mg and debossing for 300 mg. Even though 300 mg strength of phase 3 formulation was not evaluated in the PK studies 81-0048 and 81-0049, it was evaluated in the phase 3 studies 81-0045 and 81-0062. The 300 mg strength is meant for use during the titration phase and only the 600 mg strength is used during the maintenance treatment.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical efficacy study, 81-0062 in PHN patients, and clinical pharmacology studies characterizing the formulation form the basis to support the dosing and claims for this NDA.

For final assessment of the safety and efficacy findings, Clinical review by Dr. Timothy Jiang (reviewing Medical Officer). Following is a brief summary of the Clinical Efficacy assessment provided by Dr. Timothy Jiang:

In the pivotal Phase 3 study (81-0062), 452 patients were randomized in Study 81-0062, 221 to G-ER 1800 mg daily and 231 to placebo. These patients then began a two week titration to treatment with G-ER 1800 mg or G-ER placebo dosed daily with the evening

meal for eight weeks (10 weeks total). A 1-week blinded tapering of gabapentin followed the 10-week treatment period.

The planned primary outcome measure was the average daily pain scores from the baseline week to the final week of the efficacy treatment period for patients treated with G-ER 1800 mg compared to placebo. There was statistically significantly greater reduction in pain when the G-ER group was compared to placebo. The least squares mean difference of G-ER vs. placebo was -0.49 with p-value of 0.0125, using the conservative method of imputation for missing data (BOCF). The three key secondary outcome measures (CGIC, PGIC, and DSI) did not reach statistical significance when the G-GT group was compared to placebo.

The study design, dose and dosing interval, and the endpoint selected for primary analyses, are appropriate for the proposed indication. However, the clinical relevance of the magnitude of the treatment effect (-0.49 in the 11 point scale) is questionable. In the comments made to the applicant in 2007 when the Agency rejected the applicant's (b) (4) , the Agency stated "Of note, the division's assessment of efficacy will consider the overall risk and benefit and not just statistical outcomes." The Agency's medical review at the same time noticed that the "proposed difference of (b) (4) points appears to be of questionable clinical significance".

In conclusion, Study 81-0062 showed that G-ER 1800 mg given as a single daily dose with the evening meal was associated with a statistically significant reduction from baseline in the primary endpoint, ADP score compared to placebo**.** However**,** the clinical relevance of the magnitude of the treatment effect (-0.49 in the 11 point scale) is questionable. Furthermore, analysis of the key secondary endpoints did not support findings of efficacy for G-ER. The analyses of the Clinician and Patient reported impression of changes (as secondary endpoints) did not meet the statistical significance as specified in the protocol, although the Clinician reported impression of change (p-value 0.0268) is very close to meeting the statistical significance (0.025). The sponsor did not offer explanation of why the key secondary endpoints failed to support the primary endpoint.

Of note, the efficacy appears to be driven by the US sites which contributed to the majority of subjects (57.2% of ITT). This study failed in Russia and Argentina as discussed before. The sponsor was asked to provide an explanation for the discrepancy between countries. They stated that the reduction in ADP score during the study on active therapy was more pronounced in the US subjects compared to the others (-2.5 versus -1.6 and -1.7, respectively). There were even greater differences in the placebo response (-1.7, -1.2, -2.3, respectively) in the three countries with subjects in Argentina exhibiting by far the largest placebo response, greater in fact than the response to active therapy. The Sponsor concludes that the most likely causes for large difference in placebo responses are either cultural differences and/or healthcare system differences in interactions with health professionals. As discussed earlier, the reviewer agrees that the difference in placebo response is a contributing factor to the markedly difference in the primary efficacy endpoint.

At the request of the Agency, the sponsor performed an exploratory subgroup efficacy analysis of the three key secondary endpoints for the US population and the non-US population (Study 81-0062), G-ER reached nominal statistical significance at PGIC, but not CGIC with alpha of 0.025 in US population.

The other two studies, 81-0038 and 81-0045 did not demonstrate efficacy for G-ER for the treatment of PHN.

In Phase 3 Study 81-0045, a total of 407 subjects were randomized to G-ER 1800 mg daily, as either a single evening dose or a divided (600 mg AM/1200 mg PM) dose or placebo for a total treatment period of ten weeks. The primary outcome measure was mean change in ADP diary score (baseline week to final week). BOCF imputation was used to account for missing data for the primary efficacy endpoint.. There was no statistically significant reduction in pain when the G-GT groups were compared to placebo.

In the Phase 2 Study 81-0038, a total of 158 subjects were randomized to titration over two weeks to doses of G-ER up to 1800 mg daily, as either a single evening dose or a divided (600 mg AM/1200 mg PM) dose, or placebo for an additional two weeks. The primary outcome measure was the mean change in ADP diary score (baseline week to final week). When LOCF was used as method of imputation, there was statistical difference of greater pain reduction between G-GT as asymmetric BID dosing compared to placebo. Using BOCF method of imputation, however, there are no statistical differences between the G-GT treatments and placebo

In conclusion, G-ER Tablets at 1800 mg daily for the treatment of patients with PHN met the pre-specified primary endpoint in one adequate and well-controlled clinical study (Study 81-0062). As stated in the End-of-Phase-2 meeting minutes, the sponsor was required to have only a single successful adequate and well-controlled study for the proposed indication of PHN.

Although the key secondary endpoints failed to support the primary efficacy endpoint statistically, they demonstrate a trend in favor of G-ER in Study 81-0062.

Although there is markedly difference in three countries in Study 81-0062, the primary efficacy is driven by the US subjects and the difference could be partially explained by the different placebo effect across three different countries.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Gabapentin was measured in plasma to assess the PK parameters. No gabapentin metabolites were measured as it does not undergo appreciable metabolism and is excreted unchanged in the urine.

2.2.3 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

No biological biomarker was assessed in this NDA. In the, randomized double-blind, placebo-controlled efficacy studies (81-0038, 81-0045 and 81-0062) the primary efficacy end point was the change from baseline to the end of the treatment period of the Average Daily Pain (ADP) score compared to placebo.

The Secondary endpoints includes change from baseline in

- Average Daily Sleep Interference Score (0-11 Likert scale)

- Patient Global Impression of Change
- Clinician Reported Global Impression of Change.

2.2.4 Exposure Response

2.2.4.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

No formal PK/PD studies were conducted in this NDA to establish the relationship between exposure and response/efficacy. The pivotal efficacy study 81-0062 provides evidence of efficacy for this product.

2.2.4.2 What are the characteristics of the dose-systemic exposure relationships for safety?

No formal PK/PD study was conducted in this NDA to establish the relationship between exposure and safety. The pivotal efficacy study 81-0062 provides evidence of safety for this product.

2.2.4.3 Does this Drug Prolong the QT or QTc Interval?

No formal QTc study was conducted in this NDA to establish the effect of gabapentin on QTc.

2.2.5 What are the general PK characteristics of the drug?

Gabapentin is absorbed from the small intestine by a saturable L-amino acid transport system. This saturable uptake transporter is reportedly responsible in the less-than-proportional increase in bioavailability with increasing doses.

Gabapentin is not bound to plasma proteins. It is not appreciably metabolized in humans, does not induce or inhibit hepatic metabolism, and is eliminated unchanged by renal excretion with a t1/2 of 5 to 7 hr, which is unaffected by dose or multiple dosing. The median Tmax for Neurontin is 2h (range 1-5h) whereas for G-ER formulation it is 8h (range 3-12h). Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. Because the elimination of gabapentin is entirely renal, patients with renal insufficiency usually need lower dosages and less frequent dosing.

2.2.5.1 What are the single dose and multiple dose PK parameters?

See below in section 2.5.1

2.2.5.2. What are the characteristics of drug absorption? Are G-ER PK parameters dose proportional?

From Neurontin package insert, it is known that gabapentin bioavailability is not dose proportional i.e., as dose is increased, bioavailability decreases. In the absorption of gabapentin from small intestine, an L-amino acid transport system is involved, which is saturable. This saturable transporter is reportedly responsible for less than dose-proportional increase in gabapentin exposure with increasing doses.

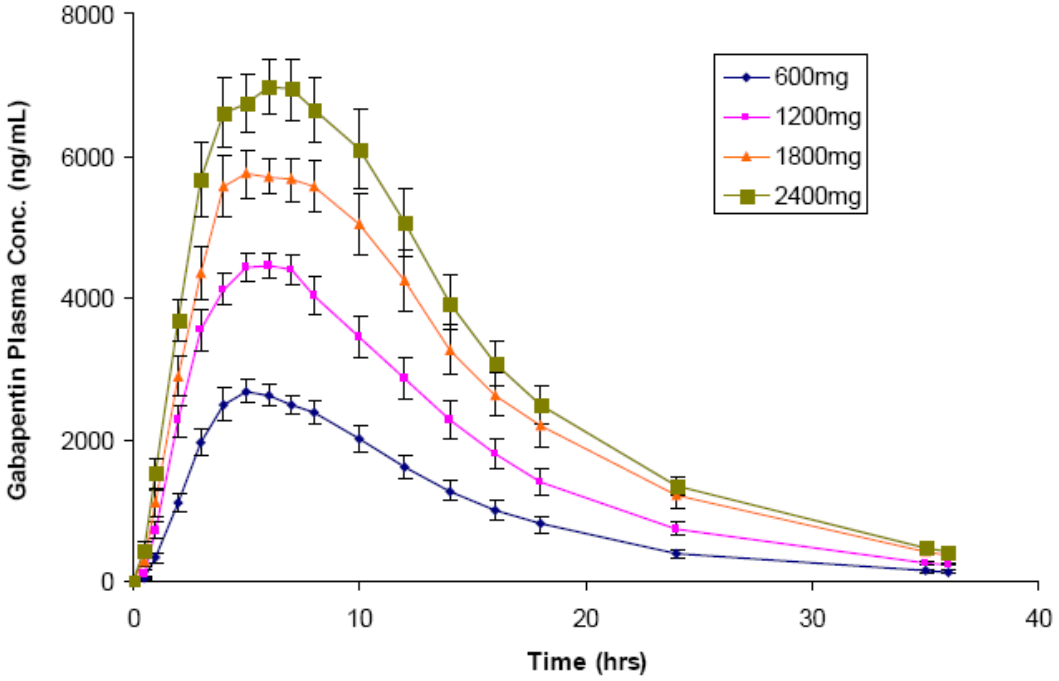
For G-ER, sponsor conducted a single dose, 4-period, crossover dose-proportionality study in 19 healthy volunteers, to evaluate the PK and dose proportionality of four dose levels of G-ER: 600 mg, 1200 mg (600 mg x 2), 1800 mg (600 mg x 3), and 2400 mg (600 mg x 4). G-ER formulations were administered after ~ 500-600 calorie, moderate fat (approximately 40% of the calories from fat) content meal. This study was conducted with phase 2 formulation.

Single oral doses of G-ER from 600 mg to 2400 mg resulted in less than proportional increases in both AUC and C_{max} (Figure 2.2.5.2). Relative bioavailability of gabapentin decreased with increasing dose. The AUC normalized to dose (multiples of 600 mg) decreased from the 600 mg dose (100%) to 89% for 1200 mg, 85% for 1800 mg, and 76% for 2400 mg. The Cmax normalized to dose (multiples of 600 mg) decreased from the 600 mg dose (100%) to 85% for 1200 mg, 76% for 1800 mg, and 67% for 2400 mg (Table 2.2.5.2).
For the proposed PHN dose of 1800 mg relative bioavailability of G-ER equals 85% of the 600 mg dose.

Table 2.2.5.2 Dose Proportionality of G-ER

PK Parameter	Geometric Mean (%CV) (n 19)			
	600 mg	1200 mg	1800 mg	2400 mg
Dose normalized AUC0-t(ng·hr/mL)	34264 (32)	30276(34)	28949(32)	25938(30)
Dose normalized Cmax (ng/mL)	2840 (26)	2413 (21)	2159 (26)	1899 (27)
Tmax (hr) (median)	6 (4-10)	6 (3-12)	6 (4-12)	7 (3-10)
T1/2 (hr)	6 ± 1	7 ± 1	7 ± 1	7 ± 2

Figure 2.2.5.2. Mean (±SEM) gabapentin plasma concentration-time profiles after single dose administration of 4 different doses of G-ER in dose



2.3 Intrinsic Factors

2.3.1 Does weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

No formal studies were conducted in special populations in this NDA. The single dose (G-ER, 600 mg) PK data from studies 81-0040, 81-0044, 81-0048, and 81-0050 were used to evaluate the gender, race and age effects. For G-ER dosing in renally impaired patients, sponsor proposed dosing based on modeling and simulations (study report 85-0009).

For gastro-retentive G-ER formulation the dosage form functionality depends on administration with food. In addition, the fat content in meals affects the rate and extent for absorption of G-ER, which increase with increases in fat% in meals. To evaluate the gender, race and age effects on G-ER PK parameters, the underlying data was divided into two groups i.e., 40% and 50% fat content in meals groups. In studies 81-0040 and 81-0044, G-ER was administered after a meal containing 40% fat, while in studies 81-0048 (high fat meal arm) and study 81-0050 G-ER was administered after a meal containing 50% fat.

2.3.1.1. Gender

Similar to the Neurontin®, no clinically significant gender-related differences was observed for G-ER that warrant dosage adjustment.

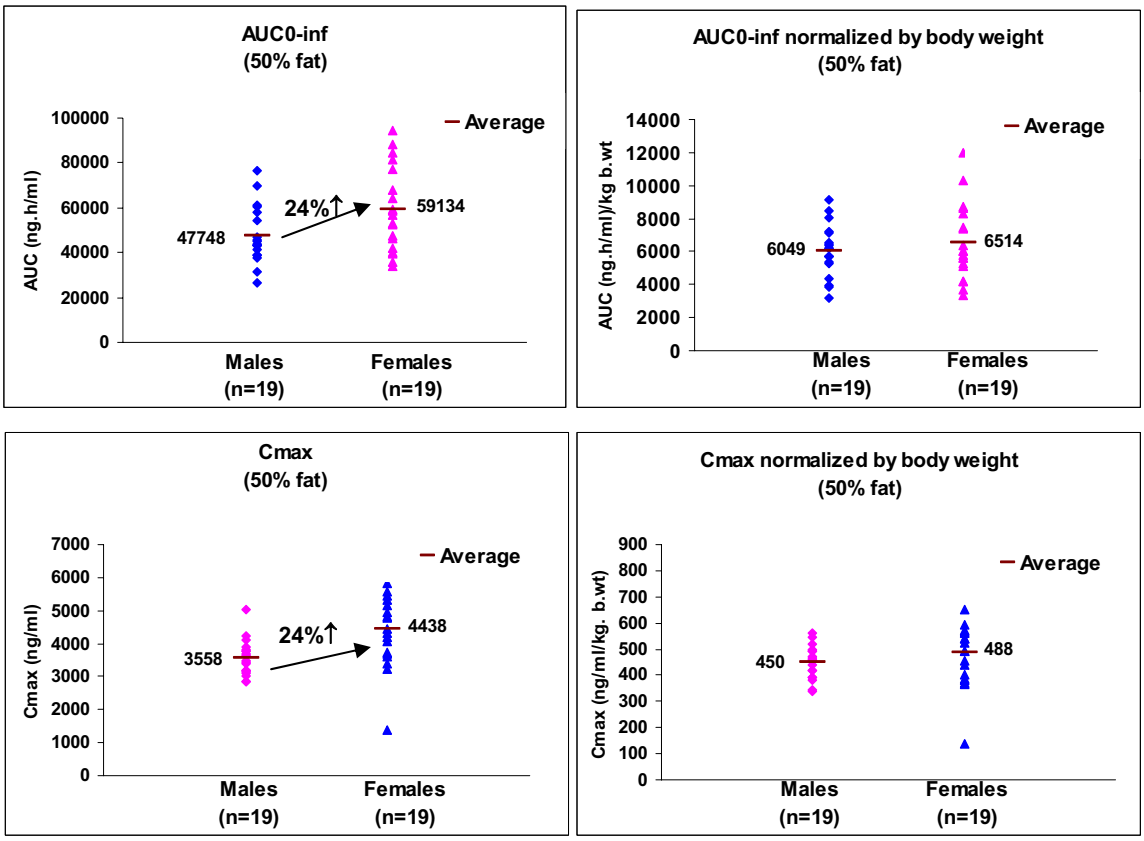
The single dose PK studies data (81-0040, 81-0044, 81-0048, and 81-0050), which included a reasonably equal ratio of male and female subjects were used to compare the gender differences. The absolute and weight normalized AUC and Cmax following G-ER administration in male and female subjects after 40% and 50% fat meals is shown in the Table 2.3.1.1. Figure 2.3.11 shows the gender effects of G-ER PK after 50 % fat meals.

The absolute values of AUC and Cmax for G-ER were ~25% higher in females compared to that of males in both 40 % and 50% fat content groups. However, when the AUC and Cmax were body-weight normalized, gender differences were greatly reduced [(Table 2.3.1.1 and Figure 2.3.1.1. (50% fat group)]. The mean ± SD weights of females and males in both fat content groups were 67 ± 8 kg and 78 ± 9 kg, respectively.

Table 2.3.1.1: Summary of G-ER PK parameters (absolute and weight normalized) by gender after 40% and 50% fat meals.

PK Parameter	40 % fat content in meals		50% fat content in meals	
	Male (n 27)	Female (n 7)	Male (n 19)	Female (n 19)
AUC (ng·hr/mL) Arithmetic mean ± SD	37055 ± 11169	46014 ± 13164	47748 ± 12707	59134 ± 1878
Weight normalized AUC	4952 ± 1663	5258 ± 1918	6049 ± 1575	6514 ± 2276
Cmax (ng/ml) Arithmetic mean ± SD	2927 ± 713	3953 ± 831	3558 ± 538	4438 ± 1143
Weight normalized Cmax	388 ± 93	444 ± 95	450 ± 63	488 ± 138
$T_{1/2}$ (h)	6.6 ± 1.3	6.1 ± 2.1	6.2 ± 1.4	5.0 ± 1.0

Figure 2.3.1.1: G-ER absolute and weight normalized AUC and Cmax in males and females after a 50% fat meal. The mean ± SD weights of females (n 19) and males (n 19) are 66 ± 7 kg and 76 ± 10 kg, respectively.



2.3.1.2. Race

For G-ER, PK differences due to race have not been studied.

To evaluate the ethnic differences, if any, on G-ER-PK, the data from single dose PK studies, 81-0040, 81-0044, 81-0048, and 81-0050 were used. The PK of gabapentin following G-ER administration after a meal containing 40% of its calories from fat in Caucasians, Blacks, and Hispanics are presented in Table 2.3.1.2a (Studies: 81-0040 and 81- 0044). No Asian subjects were enrolled in these two studies. The PK of gabapentin following G-ER administration after a meal containing 50% of its calories from fat in Caucasians, Blacks, Hispanics and Asians are presented in Table 2.3.1.2b and Figure 2.3.1.2 (Studies: 81-0048 and 81- 0050).

Although small differences in AUC and C_{max} were observed, there was no clear ethnic pattern. The results of these analyses do not indicate any clinically significant differences in gabapentin PK following G-ER tablets due to differences in ethnicity.

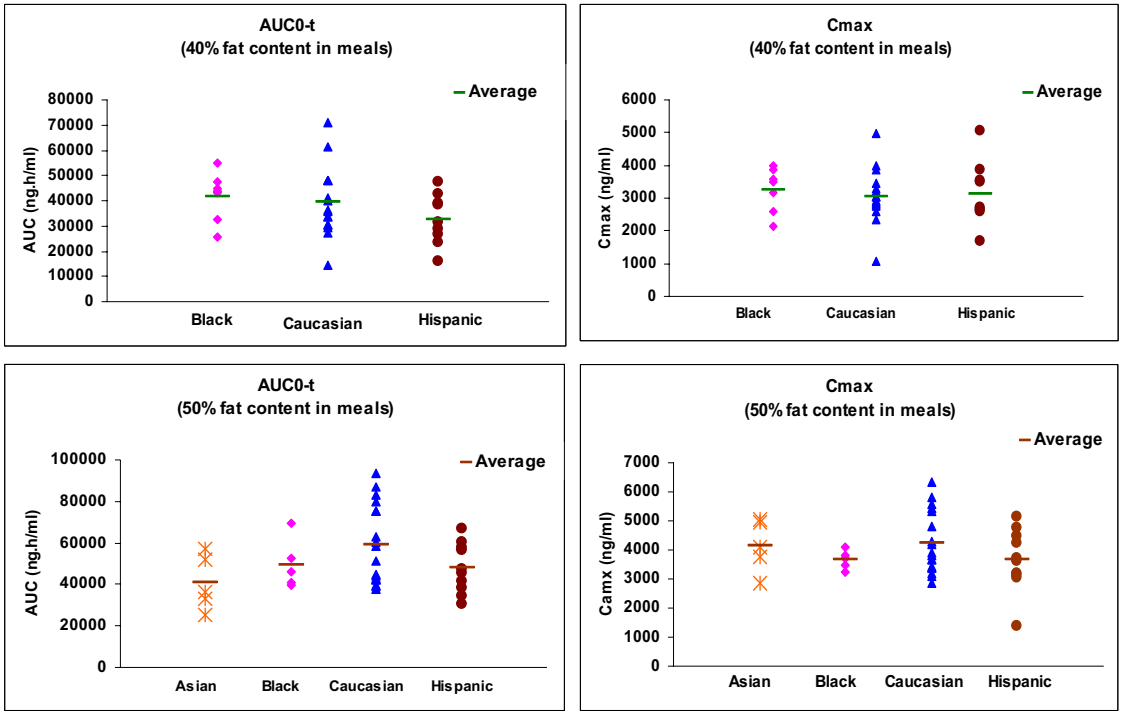
Table 2.3.1.2a: G-ER PK parameters by ethnicity: subjects completing treatments in studies 81-0040 and 81-0044 (fat content: 40%)

PK Parameter (Arithmetic Mean ± SD)	G-ER 600 mg		
	Caucasian (n 16)	Black (n 7)	Hispanic (n 9)
$AUC_{0\ inf}$ (ng·hr/mL)	40555 ± 13882	43107 ± 9718	33865 ± 9853
Cmax (ng/mL)	3061± 831	3264± 682	3134± 971
t½ (hr) Median (Min, Max)	6.4 (4.7, 10.3)	6.44 (5.7, 9.5)	6.15 (4.2, 9.3)

Table 2.3.1.2b: G-ER PK parameters by ethnicity: subjects completing treatments in studies 81-0048 and 81-0050 (fat content: 50%)

PK Parameter (Arithmetic Mean ± SD)	G-ER 600 mg			
	Caucasian (n 18)	Black (n 5)	Hispanic (n 10)	Asian (n 5)
$AUC_{0\ inf}$ (ng·hr/mL)	60000 ± 19025	50626 ± 12090	48854 ± 11890	41820 ± 13302
Cmax (ng/mL)	4234 ± 1060	3674 ± 328	3668± 1086	4131 ± 898
t½ (hr) Median (Min, Max)	5.7 (4.4, 9.8)	5.4 (4.3, 7.1)	4.7 (3.4, 7.9)	4.8 (4.0, 5.5)

Figure 2.3.1.2: G-ER AUC and Cmax in different ethnic groups after a 40% and 50% fat meals. Data from the PK studies 81-0040, 81-0044, 81-0048, and 81-0050 were used to construct the figure.



2.3.1.3. Age

Renal excretion is the predominant elimination pathway of gabapentin. Since renal function decreases with age, gabapentin clearance may possibly decrease with age, resulting in higher exposure to the drug in the elderly.

Neurontin package insert indicates that apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those less than 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.

The age effect was evaluated using data from studies, 81-0040, 81-0044, 81-0048, and 81-0050 based on the fat% in meals. Figure 2.3.1.3a depicts the individual $AUC_{0-\infty}$ vs. age for subjects in studies 81-0040 and 81-0044 (40% fat content), while 2.3.1.3b shows the same parameters in subjects included in studies 81-0048 and 81-0050 (meal containing 50% of its calories from fat). The age of the subjects in the PK studies on G-ER ranges from 20 to 65 years old.

Figure 2.3.1.3a Individual gabapentin $AUC_{0-\infty}$ vs. Age in subjects receiving a 600 mg G-ER Tablet following a meal containing 40% fat (studies 81-0040 and 81-0044).

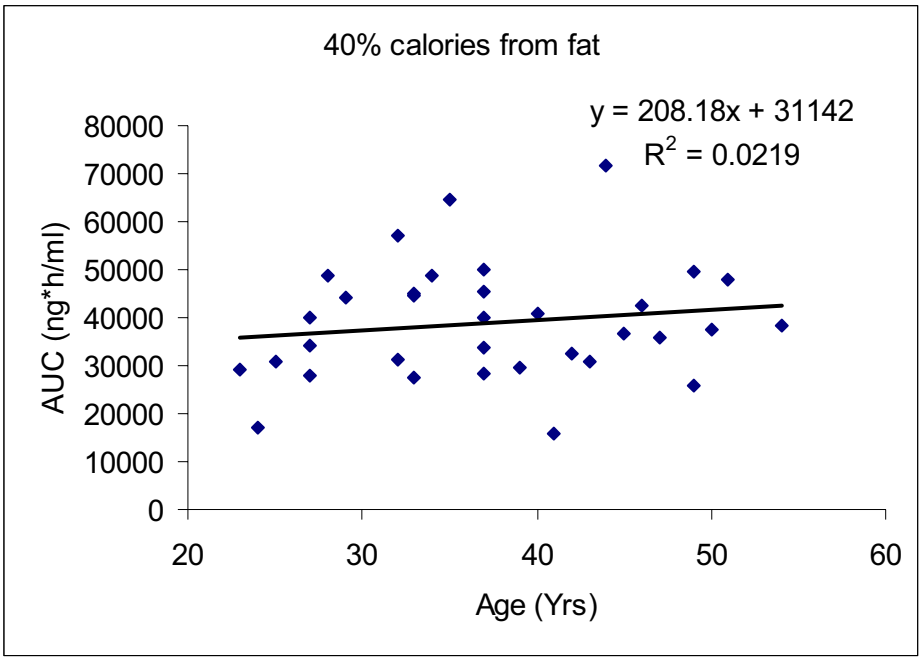
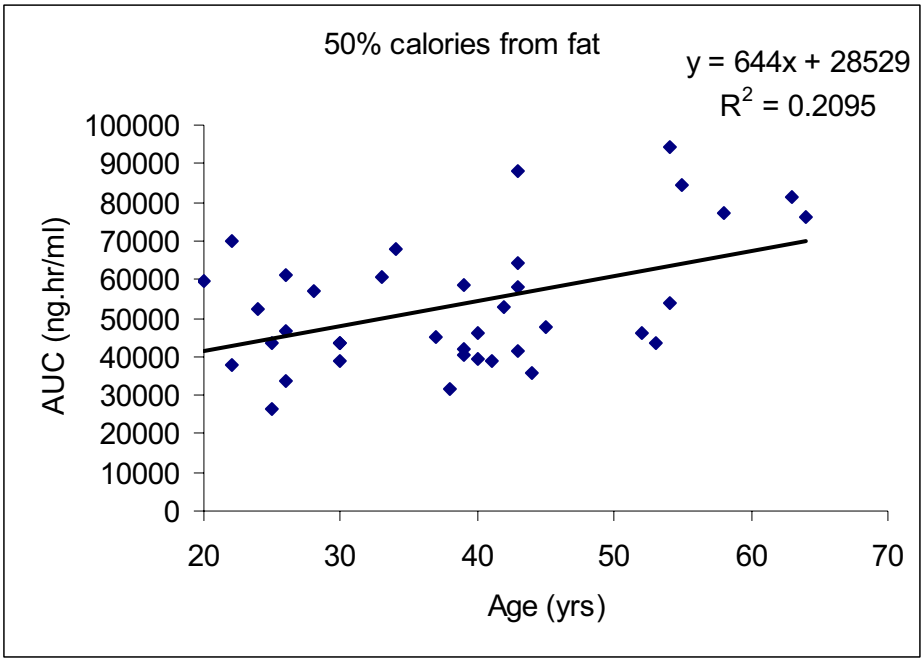


Figure 2.3.1.3b Individual gabapentin $AUC_{0-\infty}$ vs. Age in subjects receiving a 600 mg G-ER Tablet following a meal containing 50% fat (studies 81-0048 and 81-0050).



2.3.1.4. Renal Impairment

Renal excretion is the predominant elimination pathway of gabapentin. Following intravenous administration, gabapentin plasma and renal clearances were approximately equal to creatinine clearance. Because gabapentin is cleared primarily by the kidney, renal impairment is likely to increase the exposure to this drug. In patients with impaired renal function, gabapentin clearance is markedly reduced and dosage adjustment is necessary.

For G-ER, no dedicated studies in renal impaired patients were conducted. The effect of decreased renal function on gabapentin pharmacokinetics and dose recommendations was addressed by the sponsor using modeling and simulations (see pharmacometrics review by Dr. Bhattaram, Ph.D. for additional details). Dr. Bhattaram's review indicated that the simulations conducted by the sponsor is acceptable in the patients with creatinine clearance of > 30 mL/min and is not acceptable for the patients with creatinine clearance range of 15-30 mL/min. In patients with creatinine clearance of 15-30 mL/min, sponsor proposed a starting and maintenance dose of (b) (4) . In this situation, patients will be starting on their final dose and will not have the opportunity to be titrated to build tolerability to the side effects such as dizziness and somnolence. Based on Agency's assessment of the simulations, proposed dosing of G-ER in renally impaired patients based on creatinine clearance are:

- 1800 mg in patients with creatinine clearance of > 60 mL/min
- 600 to1800 mg in patients with creatinine clearance of 30-60 mL/min.

In patients with a creatinine clearance of 15-30 mL/min or in patients receiving hemodialysis, G-ER should not be administered

In addition, the following language for patients with creatinine clearance < 30 or in those receiving hemodialysis is to be added to Patients with Renal Impairment in Dosage and Administration Section

Sponsor proposed changes are in *italicized text*, reviewer suggested additions are in **bold underlined text and deletions are strike-through text**.

Patients with Renal Impairment:
In patients with stable renal function, creatinine clearance (CCr) can be reasonably well estimated using the equation of Cockcroft and Gault:

For females CCr (0.85)(140-age)(weight)/[(72)(SCr)]

For males CCr (140-age)(weight)/[(72)(SCr)]

where age is in years, weight is in kilograms and SCr is serum creatinine in mg/dL.

The dose of GRALISE should be adjusted in patients with reduced renal function, according to Table 1. **All patients must initiate GRALISE at a daily dose of 300 mg. Dose increments in patients with reduced renal function must be individualized based on tolerability and desired clinical benefit.**

Table 1: TRADENAME Dosage Based on Renal Function

Once-daily dosing	
Creatinine Clearance (mL/min)	*GRALISE Dose (once daily with evening meal)*
≥60	*1800 mg*
30 60	*600 mg to 1800 mg*
15-30	(b) (4) **GRALISE should not be administered**
In patients receiving hemodialysis	**GRALISE should not be administered**

2.3.1.5 Pediatrics

Sponsor has requested a full waiver for the safety and efficacy studies for G-ER in pediatric subpopulations. The pediatric age group for which a waiver is requested is 0-17 years.

The justification of waiver is "the indication studied and applied for G-ER is for the management of PHN. This disease is not prevalent in the pediatric age groups, which would make the recruitment of clinical studies impossible or highly impractical for the small number of pediatric patients". This product was discussed in the PERC meeting on November 03, 2010 and a waiver below 17 years of age was granted

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, smoking and alcohol on G-ER use were not evaluated. G-ER is labeled to be taken after meals. Hence in all clinical pharmacology and clinical studies G-ER was administered after meals. The sponsor conducted a dedicated food effect study with low and high fat contents to investigate the effect of fat % in food on the G-ER PK. This is discussed in the next section below.

2.5 General Biopharmaceutics

2.5.1 What are the single dose/multiple dose pharmacokinetics of G-ER and its relative bioavailability compared to Neurontin®?

Relative bioavailability (BA) of G-ER in-comparison to Neurontin® was evaluated in four different studies (studies 81-0008, 81-0040, 81-0049, 81-0050). Study 81-0049 was a dedicated three way cross-over study in which relative BA was evaluated after single and multiple dosing (5 days, Day 3- Day 7) in 24 healthy subjects.

Subjects received, in a randomized order, 1800 mg G-ER tablets QD (evening dose), 1800 mg G-ER tablets divided into two doses (600 mg in the morning, 1200 mg in the evening), or 1800 mg Neurontin® tablets (600 mg, TID). All doses were administered 30 minutes after a high-fat content meal (50% calories from fat).

Pharmacokinetic parameters for two G-ER dose regimens and Neurontin® after single dose and multiple dosing are presented in Table 2.5.1 and 2.5.2, respectively. The geometric means ratios (ER/IR) and the 90% confidence intervals for AUC and Cmax are shown in Figure 2.5.1a. The Day 1 and Day 8 mean gabapentin plasma concentration-time profiles following each dosage regimen are illustrated in Figure 2.5.1b.

Results of relative BA study (81-0049) comparing two dosing regimens of G-ER vs. IR formulation show comparable PK parameters. This is evident by similar values of AUC0-∞, Cmax after a single day dose (Day 1) and AUC0-24, Cmax at steady state (Day 8, five days of consecutive dosing) between G-ER and IR (Table 2.5.1 and 2.5.2). The ratios of geometric means and 90% CIs for Cmax and AUC were within 80-125% limits comparing two G-ER dose regimens vs Neurontin® after single and multiple dose administration (Figure 2.5.1). The terminal elimination half life was similar between G-ER (~8.5 h) and IR (8.4 h) (Table 2.5.1). After multiple daily dosing, G-ER showed no accumulation, similar to Neurontin®. Steady state was reached after 2 days. The trough concentrations are about 45% lower with G-ER tablets. With respect to % degree of fluctuation and % degree of swing, values for both these parameters are higher for G-ER compared to Neurontin (141 vs. 102 for % fluctuation and 456 vs. 246 for % swing parameters). It should be noted that G-ER tablet exhibiting the multiple dose pharmacokinetic characteristics as discussed above was evaluated in safety and efficacy trials 81-0045 and 81-0062.

The median Tmax relative to the last dose (Tmaxrel) was longer for G-ER compared to Neurontin® after single dose (G-ER BID- 8 hr; G ER QD-8 hr vs. IR TID- 2hr) and multiple dose (G-ER BID- 6 hr; G ER QD-8 hr vs. IR TID- 2hr) administration. The proposed dosing for the G-ER is QD with evening meals.

Table 2.5.1: Gabapentin Pharmacokinetics after Single dose administration with BID G-ER (600 mg AM +1200 mg PM), QD G-ER (1800 mg PM), and TID Neurontin® (3 x 600 mg)

Pharmacokinetic Parameter	G-ER BID (600 mg AM, 1200 mg PM)	G-ER QD (1800 mg PM)	Neurontin® TID (600 mg x 3)
$AUC_{0\infty}$ (ng·hr/mL)	144491 ± 28619	124008 ± 32144	139010 ± 32206
Cmax (ng/mL)	6997 ± 1480	7974 ± 2157	7455 ± 1496
* Tmax (hr)[b]	20 (16 - 24)	8 (4 - 12)	14 (4 - 16)
* Tmaxrel (hr)[c]	8 (4 - 12)	8 (4 - 12)	2 (1 - 4)
t1/2 (hr)	7.4 ± 1.5	9.1 ± 3.2	8.4 ± 1.9

[b] Tmax- time to reach the Cmax within 24 hr post the 1st dose on Day 1
[c] Tmaxrel is defined as the Tmax relative to the last dose
* median (min - max)

Table 2.5.2: Gabapentin Pharmacokinetics after multiple dose administration with BID G-ER (600 mg AM +1200 mg PM), QD G-ER (1800 mg PM), and TID Neurontin® (3 x 600 mg)

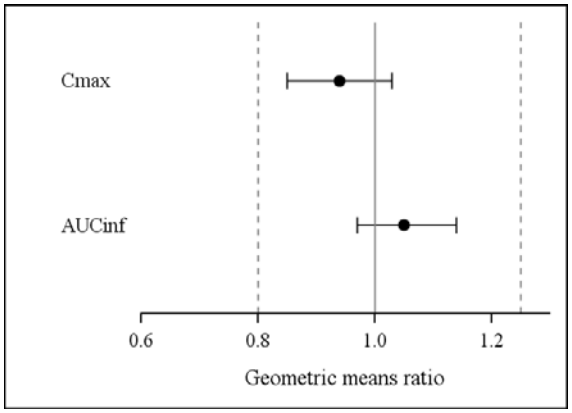
Pharmacokinetic Parameter	Arithmetic Mean ± SD		
	G-ER BID (600 mg AM, 1200 mg PM)	G-ER QD (1800 mg PM) (600 mg x 3	Neurontin® TID
AUC 0-24 (ng·hr/mL)	144605 ± 31171	132808 ± 34701	141301 ± 29759
Ctrough (ng/mL)	6097 ± 1609	2043 ± 702	3701 ± 1201
Cmax (ng/mL)	8048 ± 1819	9585 ± 2326	8536 ± 1715
Cmin (ng/mL)	3964± 1311	1842 ± 654	2588 ± 783
Cavg (ng/mL)	6025 ± 1300	5534 ± 1446	5885 ± 1242
* Tmax (hr)	18.0 (8.0 - 24.1)	8.0 (3.0 - 12.0)	8.0 (2.0 - 17.0)
* Tmaxrel (hr)	6.0 (4.0 - 12.1)	8.0 (3.0 - 12.0)	2.0 (1.0 - 5.0)
Degree of Fluctuation (%)	69± 19	141 ± 20	102 ± 14
Degree of Swing (%)	113 ± 50	456± 177	246± 79

Cmax: Maximum plasma concentration observed after dosing on Day 8
Cmin: Minimum concentration during the dosing interval
Ctrough: Pre-dose concentrations
Cavg: AUC 0-τ / τ (where: τ = 24 hours)
Tmax: Time of observed maximum concentration (Css max) relative to the initial dose
Tmaxrel: Tmax relative to the most recent dose
% Fluctuation: Degree of concentration fluctuation at steady state
[(Css max- Css min)/(Cave)] *100
% Swing: Degree of concentration swing at a steady state
[(Css max - CSS min)/ CSS min)] *100
* median (min - max)

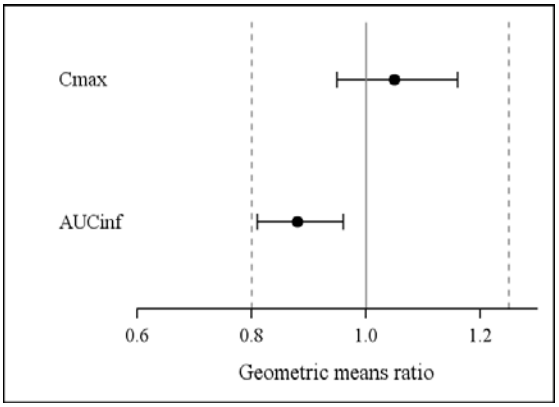
Figure 2.5.1a: Ratios of geometric means (G-ER / Neurontin®) and the 90% confidence intervals for the AUC and Cmax after single dose (Day 1) and multiple dose (Day 8) administration of G-ER and IR formulations.

Single Dose

G-ER BID vs. Neurontin® TID

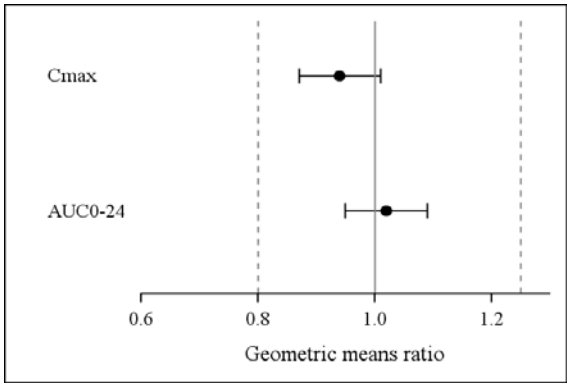


G-ER QD vs. Neurontin® TID



Multiple Dose (5 days)

G-ER BID vs. Neurontin® TID



G-ER QD vs. Neurontin® TID

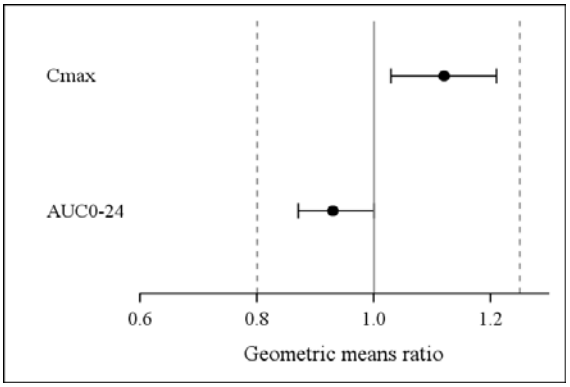
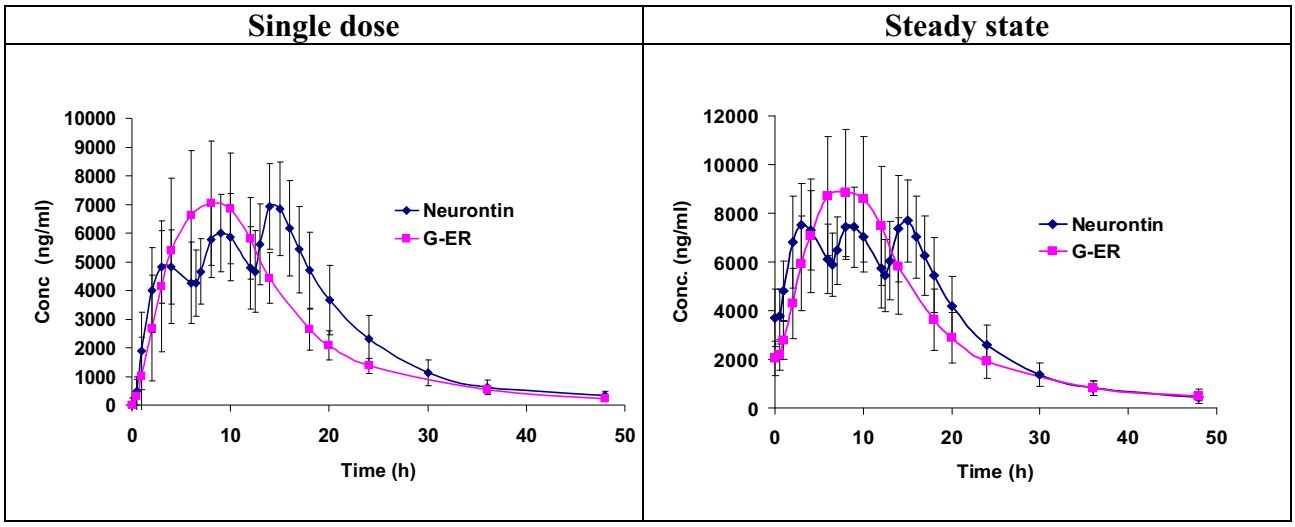


Figure 2.5.1b Mean (±SEM) Gabapentin Plasma Concentration-Time Profiles on Day 1, following G-ER (1800 mg PM) and Neurontin® (600 mg TID)



2.5.2 What is the BCS Class classification for G-ER?

Not Applicable.

2.5.3 What is the effect of food on the BA of G-ER?

For the G-ER, as the dosage form's functionality depends on administration with food, hence all PK studies were performed in the fed state. In addition, fat % in meals may affect the PK of G-ER.

Study 81-0048 was a dedicated 3 way crossover food effect study in which G-ER 600 mg was administered after fasting, low fat and high fat meals (n 22). The definition of low and high fat meals is as follows:

- Low-fat meal: < 30% of calories from fat, 836 cal
- High-fat meal: > 50% of calories from fat, 945 cal

The data showed that G-ER exposure increases with increase in fat content meals. Compared to the fasting conditions, the mean G-ER $AUC_{0-\infty}$ increases by 33, and 119%, respectively, after a meal containing 30%, and 50% of its calories from fat. Similarly, Cmax also increases by 33, and 84%, respectively with 30%, and 50% fat content in meals (Table 2.5.3b).

A Box Plot of AUC_{inf} and Cmax [showing the median, 75th percentile of the data set (upper hinge), 25th percentile of the data set (lower hinge), minimum, maximum and outliers] under fasting, low and high fat meals conditions were show in Figures 2.5.3a and 2.5.3b, respectively. The arithmetic mean ± SD of the PK parameters data after fasting, low and high fat meals and the fold changes are shown in the Tables 2.5.3a and 2.5.3b, respectively.

In the gastro-retentive drug delivery system, gastric retention of the formulation depends on fed state, which reflects on the time to reach peak concentration (Tmax) of drug. Accordingly, G-ER Tmax is different between fasting and different fed conditions.

In the fasting conditions, the median G-ER Tmax was 3.5 hr with a range of 1-10 hr whereas for Neurontin®, it was also 3.5 hrs with a smaller range of 3 5 hr. In the fed conditions (under which G-ER is to be taken), Tmax values were prolonged as fat % of meal increased. The median T_{max} was 6.0 hr (range 3-10) with 30% fat, and 9.0 hr (range 4 12) with 50% fat in meals (Table 2.5.3a and Figure 2.5.3c). While the gastro-retentive G-ER tablets showed an effect on the absorptive phase of the pharmacokinetics, the elimination phase of gabapentin, as measured by the terminal half-life, was not much affected. In the fasting conditions, the longest average G-ER half-life was 8.7 ± 4.0 hr. In fed conditions, $T_{1/2}$ was 5.6 ± 1.3 hr with 50 % fat, which is similar to Neurontin® $T_{1/2}$ of 6.5 ± 1.3 hr with 40% fat content (study 81-0040).

Table 2.5.3a: Summary of G-ER PK parameters in fasted and fed conditions with different fat percentages in meals.

PK Parameter	Arithmetic Mean ± SD		
	Fasting (n 22)	Low-fat (836 cals, < 30% fat) (n 22)	High-fat (945 cals > 50% fat (n 38)
$AUC_{0\ t}$ (ng·hr/mL)	21966 ± 12432	31399 ± 12439	52434 ± 16757
$AUC_{0\ \infty}$ (ng·hr/mL)	24430 ± 12478‡	32435 ± 12467	53441 ± 16779
Cmax (ng/mL)	2175 ± 923	2902 ± 749	3998 ± 988
Tmax (hr)*	3.5 (1-10)	6 (3-10)	8 (4-12)
t1/2 (hr)	8.7 ± 4.0‡	6.8 ± 1.9	5.6 ± 1.3

* median (min max)
‡ n 19

Table 2.5.3b: Ratio of means of G-ER $AUC_{0-\infty}$ and Cmax comparing low and high fat % meals vs. fasting conditions.

Treatment comparison	PK -parameter fold change	
	$AUC_{0-\infty}$	Cmax
Low fat / Fasting	1.33	1.33
High fat / Fasting	2.19	1.84

Figure 2.5.3a: Box plot showing the effect of low and high fat percentages in meals vs. fasted conditions on $AUC_{0-\infty}$ G-ER (600 mg) (n 22).

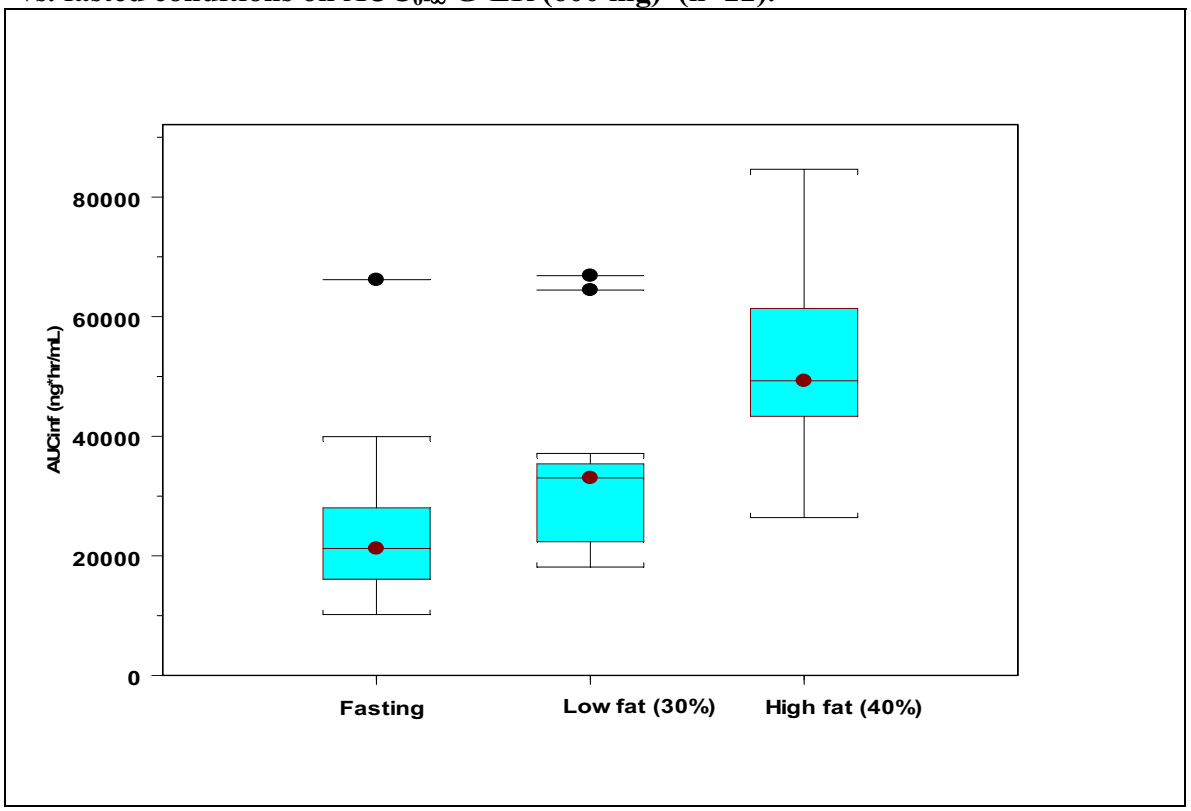


Figure 2.5.3b: Box plot showing the effect of low and high fat percentages in meals vs. fasted conditions on Cmax of G-ER (600 mg) (n 22).

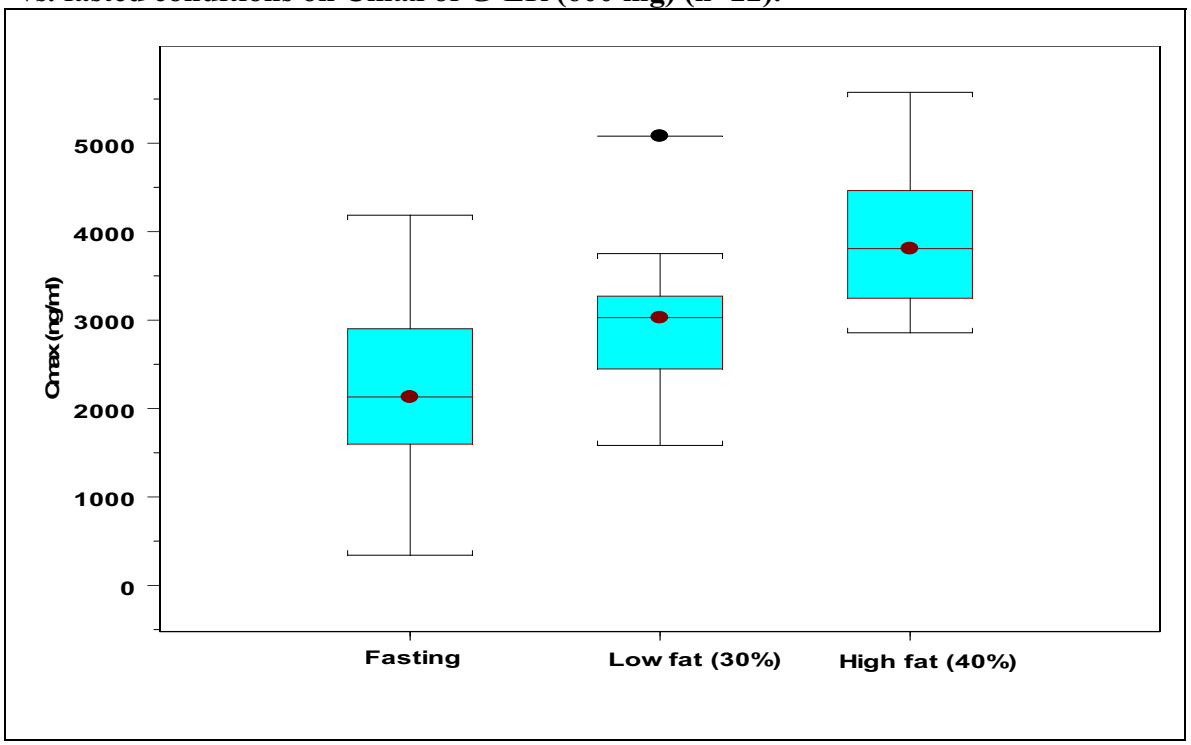


Figure 2.5.3c: Box plot showing the effect of low and high fat percentages in meals vs. fasted conditions on Tmax of G-ER (600 mg) (n 22).

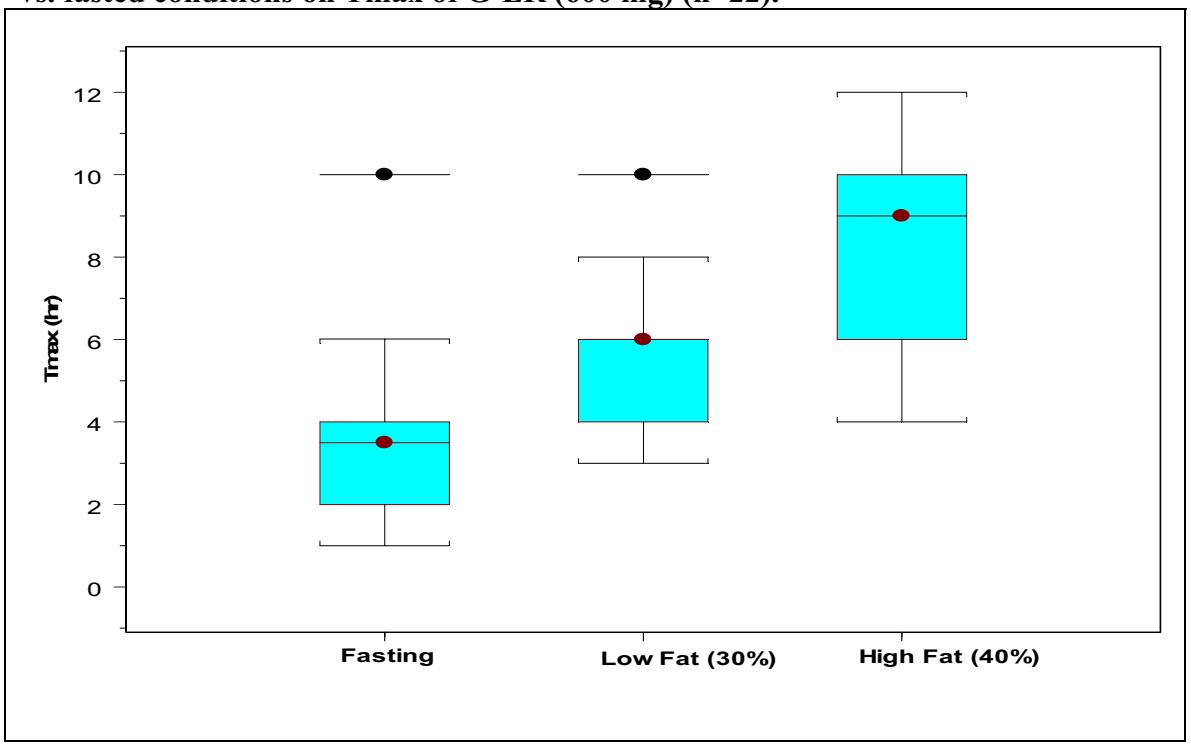
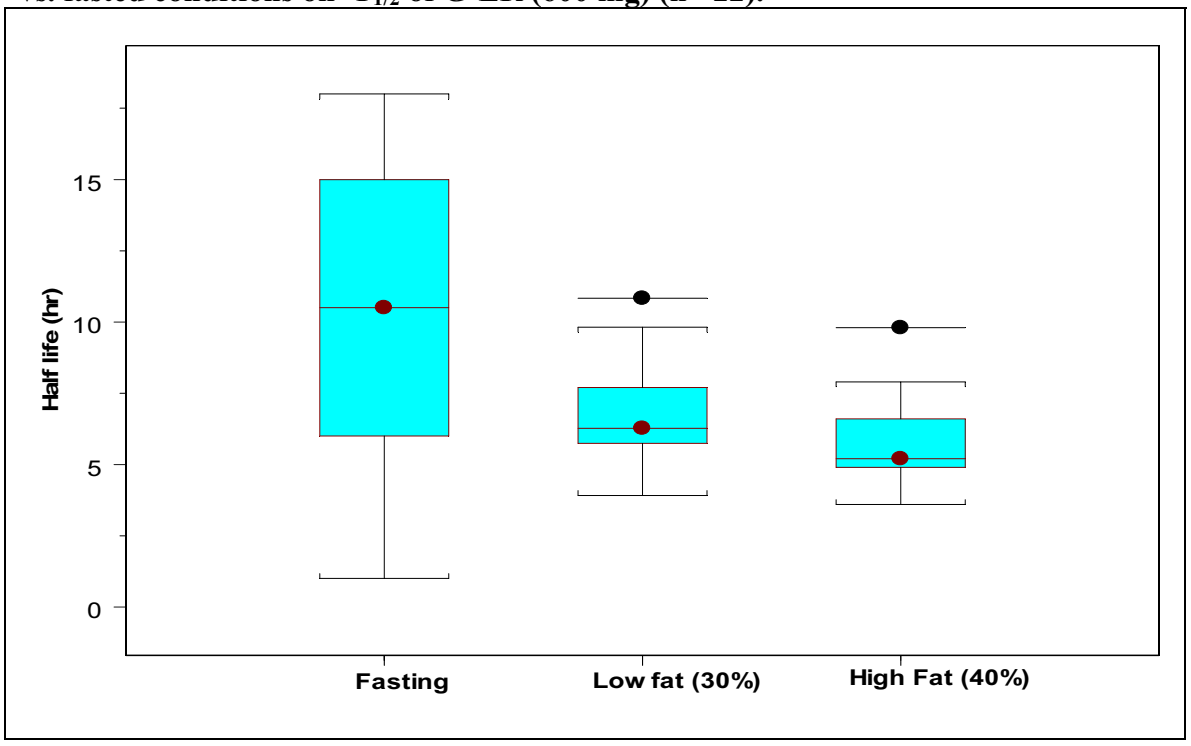


Figure 2.5.3d: Box plot showing the effect of low and high fat percentages in meals vs. fasted conditions on $T_{1/2}$ of G-ER (600 mg) (n 22).



The observed food (fat) effect on G-ER exposure and Cmax does not warrant timing of product administration in relation to meal consumption. Sponsor is appropriately proposing that G-ER formulation should be taken with evening meal. By specifying that the product be taken with evening meal (as opposed to generic term food), some of the variability in meal composition likely to be encountered is reduced as evening meals generally tend to be more elaborate than a simple snack.. As such, sponsor's labeling language on food effect is acceptable with the following reviewer proposed changes.

Sponsor proposed changes are in *italicized text*, reviewer suggested additions are in **bold underlined text**.

"GRALISE should be taken with evening meals. If it is taken on an empty stomach, the bioavailability will be substantially lower. *Administration of GRALISE with food increases the rate and extent of absorption of gabapentin compared to* **that of** *the fasted state. C_{max} of gabapentin increases 33-84% and AUC of gabapentin increases 33-118% with food depending on the fat content of the meal.*

2.5.4 Does G-ER 300 mg establish dosage form proportionality in PK to G-ER 600 mg?

Study 81-0040 was a single dose, randomized, dosage form (strength) proportionality study conducted in 15 healthy volunteers to evaluate the bioequivalence of G-ER 300 mg (2 different formulations, Lots 1079 and 1090, respectively) and G-ER 600 mg (Lot 1082) and to compare the pharmacokinetic parameters of these formulations to Neurontin. This study was conducted with phase 2 formulation.

Dosage form (strength) proportionality was established between the 600 mg formulation (Lot 1082) and one of the 300 mg formulations (Lot 1079, administered as 300 mg x2). With the dosage form proportionality of these two strengths established, the formulations for Lots 1079 and 1082 were selected for further development.

Table 2.5.4: Gabapentin Pharmacokinetic Parameters (Study Report: 81-0040)

PK Parameter	Arithmetic Mean ± SD (n 15)			
	G-ER 1 x 600 mg (Lot # 1082)	G-ER 2 x 300 mg (Lot # 1079)	G-ER 2 x 300 mg (Lot # 1090)	Neurontin 1 x 600 mg
AUC0-∞ (ng·hr/mL)	40515 ± 12264	43172 ± 13576	38573 ± 15182	42694 ± 8857
Cmax(ng/mL)	3362 ± 890	3416 ± 879	2982 ± 1054	4367 ± 1054
Tmax(hr)[a]	6.0 (3.0 - 10.0)	6.5 (4.5 - 10.0)	5.0 (3.5 - 10.0)	3.5 (2.0 5.0)
t1/2 (hr)	6.6 ± 1.6	6.7 ± 1.8	6.7 ± 2.0	6.5 ± 1.3

[a] Median (min - max)

2.5.6 Was the to-be-marketed formulation used in the PK/Clinical trials?

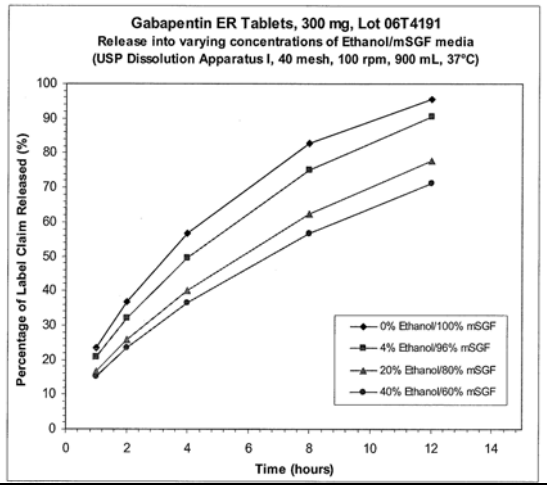
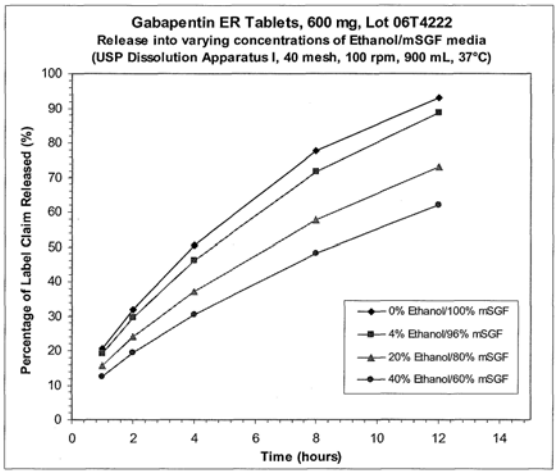
The to-be marketed G-ER 300 mg formulation differs from the Phase 3 formulation in debossing and whereas to- be marketed G-ER 600 mg differs in debossing and color which are not significant changes.

The formulations used in clinical pharmacology and clinical studies are shown in section 2.1.1. Phase 2 and Phase 3 formulations were used in the clinical and clinical pharmacology studies. The studies in which Phase 2 formulation was used were dosage-form proportionality, dose proportionality and Phase 2 efficacy studies. The studies in which Phase 3 formulation was used were single dose, multiple dose, relative bioavailability, food effect and Phase 3 efficacy studies. The to-be marketed G-ER 300 mg formulation differs from the Phase 3 formulation in debossing and whereas to- be marketed G-ER 600 mg differs in debossing and color.

2.5.7. Is there a potential for dose dumping in the presence of alcohol?

The in-vitro alcohol effect on G-ER release is being reviewed by Dr. Sandra Suarez, Biopharmaceutics reviewer of ONDQA and the final assessment on this aspect is deferred to her. However, the in-vitro data reported by the sponsor does not indicate a potential for dose-dumping in alcohol (figure 2.2.7 a).

Figure 2.2.7a: Gabapentin cumulative release profile of G-ER 300 and 600 mg Tablets in hydro-alcoholic release media.

G-ER 300 mg	G-ER 600 mg
	

2.6 Analytical Section

2.6.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

The plasma concentrations of gabapentin were analyzed using validated HPLC-MS/MS assays. The range of calibrators and QCs used for studies were:

- Calibrators: 75, 150, 300, 600, 1200, 2400, 4800, 9600 ng/ml
- Quality controls: 225, 1800 and 7200 ng/ml

The accuracy and precision for QCs for both assays were within the acceptable range of 100 ± 15%.

3.0 Labeling Comments

Reviewer comments:
This proposed labeling is acceptable from the clinical pharmacology perspective with the following changes to the:

- Food effect in Pharmacokinetics Section
- Patients with Renal Impairment in Dosage and Administration Section

Sponsor proposed changes are in *italicized text*, reviewer suggested additions are in **bold underlined text and deletions are strike-through text**.

Food effect:
"**GRALISE should be taken with evening meals. If it is taken on an empty stomach, the bioavailability will be substantially lower**. *Administration of GRALISE with food increases the rate and extent of absorption of gabapentin compared to* **that of** *the fasted state. C_{max} of gabapentin increases 33-84% and AUC of gabapentin increases 33-118% with food depending on the fat content of the meal.*

Patients with Renal Impairment:
In patients with stable renal function, creatinine clearance (CCr) can be reasonably well estimated using the equation of Cockcroft and Gault:

For females CCr (0.85)(140-age)(weight)/[(72)(SCr)]
For males CCr (140-age)(weight)/[(72)(SCr)]

where age is in years, weight is in kilograms and SCr is serum creatinine in mg/dL.

The dose of GRALISE should be adjusted in patients with reduced renal function, according to Table 1. **All patients must initiate GRALISE at a daily dose of 300 mg. Dose increments in patients with reduced renal function must be individualized based on tolerability and desired clinical benefit.**

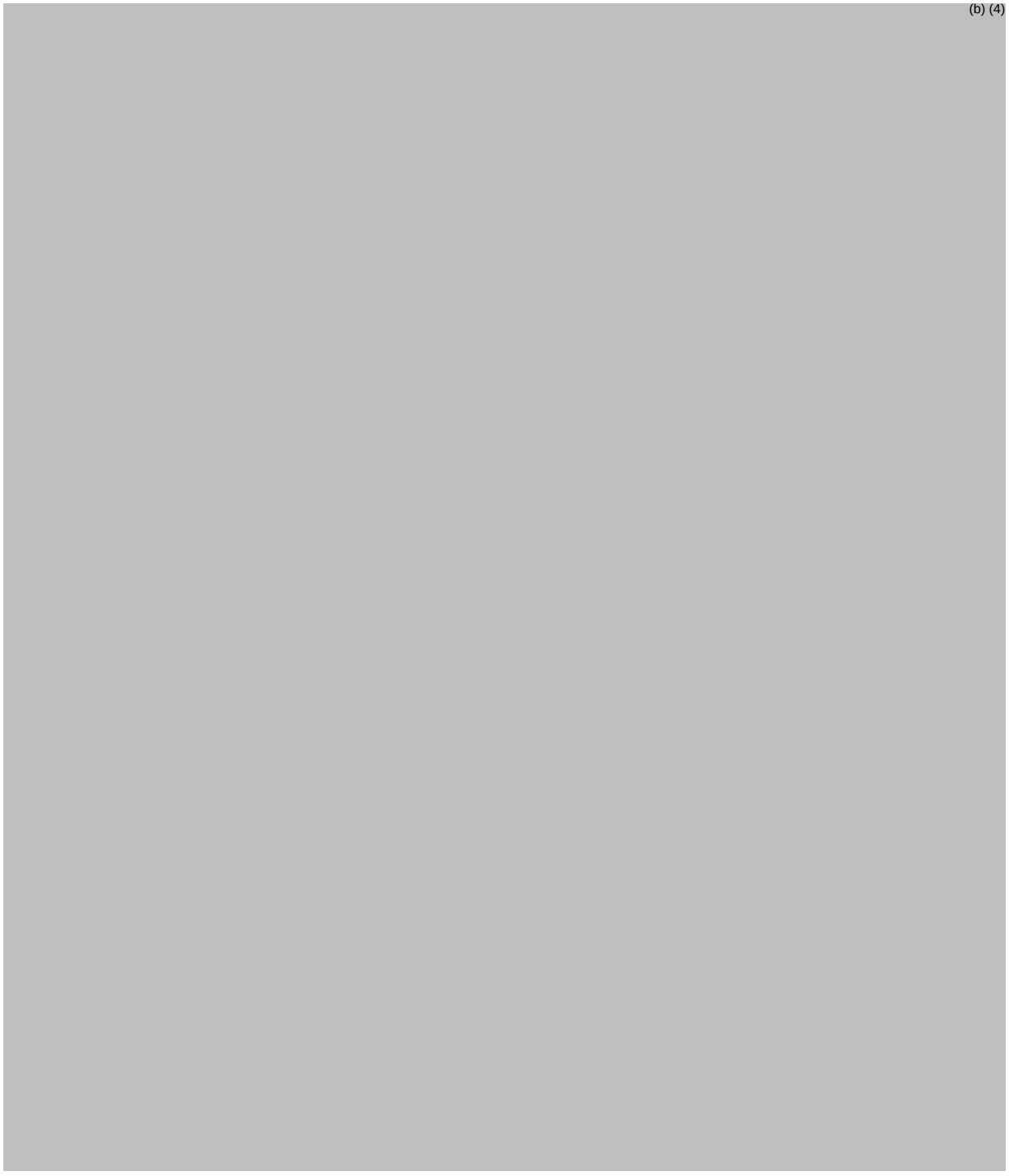
Table 1: GRALISE Dosage Based on Renal Function

Once-daily dosing	
Creatinine Clearance (mL/min)	*GRALISE Dose (once daily with evening meal)*
≥60	*1800 mg*
30 60	*600 mg to 1800 mg*
15-30	(b) (4) **GRALISE should not be administered**
In patients receiving hemodialysis	**GRALISE should not be administered**

4.0 Appendices

4.1 Sponsor's Proposed Label

(b) (4)



23 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

4.2 Pharmacometric Review:

APPEARS THIS WAY ON ORIGINAL.

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key question.

1.1.1 Is the proposed dosing regimen for gabapentin-ER formulation in patients with varying degrees of renal function acceptable?

The proposed dosing regimen (Table 1, Table 2) for gabapentin-ER (G-ER) formulation in patients with creatinine clearance greater than 30 mL/min is acceptable. However, the dosing recommendations for patients with creatinine clearance between 15 and 30 mL/min must be modified. Patients with creatinine clearance between 15 and 30 mL/min would be administered an initial once-daily dose (b) (4) G-ER formulation in comparison to once-daily 200 mg Neurontin® immediate release formulation as shown in Table 3. The higher initial once-daily dose could lead to tolerability issues with G-ER formulation in comparison to Neurontin® immediate release formulation in patients with creatinine clearance between 15 and 30 mL/min.

Table 1. G-ER dosing regimen (initiation and titration) in patients with creatinine clearance greater than or equal to 60 mL/min.

	Day1	Day2	Day3-6	Day7-10	Day11-14	Day15
Daily Dose (mg)	300	600	900	1200	1500	1800

Table 2. Sponsor proposed G-ER dosing regimen (maintanence dose after titration) in patients with varying degrees of renal function

Renal Function Creatinine Clearance (mL/min)	G-ER dose, mg (Once-daily with evening meal)
≥60	1800
30-60	600 to 1800

(b) (4)

Table 3. Comparison of Neurontin® and G-ER (Gabapentin-ER) dosing guidelines in patients with various degrees of renal function.				
Renal Function Creatinine Clearance (mL/min)	Neurontin® Total Daily Dose Range (mg/day)		Gabapentin-ER Total Daily Dose Range (mg/day)	
≥60	900-3600	300-1200 TID	1800	3x600 mg QD
>30-59	400-1400	200-700 BID	600-1800	1x-3x600mgQD
>15-29	200-700	200-700 QD	[redacted] (b) (4)	
15	100-300	100-300 QD	No guidelines proposed	
	Post-Hemodiaysis Supplemental Dose (mg)		Post-Hemodiaysis Supplemental Dose (mg)	
Hemodialysis	125-350 mg after each post-hemodialysis dose		No guidelines proposed	

1.2 Recommendations

The proposed dosing guidelines for G-ER formulation are shown in Table 4.

Table 4. Reviewer proposed G-ER dosing regimen (maintanence dose after titration) in patients with varying degrees of renal function

Renal Function Creatinine Clearance (mL/min)	G-ER dose, mg (Once-daily with evening meal)
≥60	1800
30-60	600 to 1800
15-30	Should not be administered

1.3 Label Statements

From label Section 2.2 as shown below

2.2 Patients with Renal Impairment

In patients with stable renal function, creatinine clearance (C_{Cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:
For females C_{Cr} (0.85)(140-age)(weight)/[(72)(S_{Cr})]
For males C_{Cr} (140-age)(weight)/[(72)(S_{Cr})]
where age is in years, weight is in kilograms and S_{Cr} is serum creatinine in mg/dL.
The dose of TRADENAME should be adjusted in patients with reduced renal function, according to Table 1. All patients must initiate TRADENAME at a daily dose of 300 mg. Dose increments in patients with reduced renal function must be individualized based on tolerability and desired clinical benefit.

Table 1 in the label must be changed as shown below

Renal Function Creatinine Clearance (mL/min)	G-ER dose, mg (Once-daily with evening meal)
≥60	1800
30-60	600 to 1800
15-30	(b) (4) Should not be administered

2 PERTINENT REGULATORY BACKGROUND

Gabapentin (Neurontin®) was originally approved in December, 1993 (NDA 20-235) as adjunctive therapy in the treatment of partial seizures and was subsequently approved for the management of PHN in adults (May 2002, NDA 21-424). This application is being submitted under 505(b)(2) of the FD&C Act and relies on FDA's findings of preclinical toxicology and safety conducted for Neurontin® (NDAs 20-129, 20-235, 20-882, 21-397, 21-423, 21-424) to support this application.

Gabapentin Extended Release (G-ER) tablets 300 mg and 600 mg, are an extended release, gastric retentive formulation containing gabapentin. Similar gastric retentive formulations marketed as Glumetza®, (metformin HCl extended release tablets) and Proquin® XR (ciprofloxacin hydrochloride) have been previously approved by the FDA. G-ER 1800 mg once-daily demonstrated comparable bioavailability to Neurontin®, the immediate release product, administered 600 mg three times daily. The G-ER once-daily regimen (dosed with the evening meal) has a maximum concentration that exceeds the maximum concentration in the three times daily IR regimen but with similar AUC values.

3 RESULTS OF SPONSOR'S ANALYSIS

Gabapentin plasma concentration data from several pharmacokinetic studies involving Depomed's gabapentin extended-release (G-ER) formulation and Neurontin®, an immediate release (IR) tablet were used to construct a compartmental PK model. The resulting model incorporated non-linear bioavailability of gabapentin with increasing dose, the effect of fat content of the meal on gabapentin bioavailability, and different release profiles of the two formulations.

Complete data from 3 studies (81-0040, 81-0044, and 81-0048) were used in developing the final model. The data from a 4th study (81-0049) functioned as the validation data set.

- Study 81-0040 was a four-way crossover, open-label, single-dose study in the fed state (500-600 calories, 40% of calories from fat). Single doses of 600mg Neurontin® and three different dosage forms of G-ER, including two 300mg formulations and one 600 mg formulation, were evaluated. The study included 16 healthy volunteers, 15 of whom (8 male, 7 female) completed all the 4 study periods. Gabapentin plasma levels were measured for 48 hours following dosing on day 1. Data from the 600mg G-ER and Neurontin were used in the model building procedure.
- Study 81-0044 was a four-arm, non-randomized, open-label, single-dose study at fed state (500-600 calories, 40% of calories from fat), comparing the bioavailability of G-ER at 4 different single doses (600mg, 1200mg, 1800mg, and 2400mg). The study included 24 healthy male volunteers, 19 of who completed all 4 periods and whose data were used in the model-building process. Gabapentin plasma levels were measured for 48 hours following dosing on day 1.
- Study 81-0048 was a three-way crossover, open-label, single-dose study, investigating the pharmacokinetics of gabapentin after administration of single doses of 600mg G-ER in fasted healthy volunteers, after the ingestion of a low-fat (836 calories and less than 30% of calories from fat), and a high-fat (945 calories and more than 50% of calories from fat) meal. The study included 24 healthy male and female volunteers, of whom 22 (11 male, 11 female) completed all three study periods and whose data were used in the model-building process. Gabapentin plasma levels were measured for 48 hours following dosing on day 1.
- Gabapentin pharmacokinetics after single and multiple dosing with G-ER (bid., qd.) and an IR formulation (Neurontin; tid.) were evaluated in study 81-0049. Data from this study was intended for external model validation, to evaluate the predictive performance of the PK model. Eleven (11) male and 10 female subjects received doses of 1800mg GER (qd.; 8:00 pm), 1800mg G-ER divided into two doses (bid.; 600mg 8:00 am, 1200mg 8:00 pm), or 1800mg G-IR (tid; 600mg, 8:00 am, 2:00 pm, and 8:00 pm) on day 1 and days 4-8 in a randomized, 3-way crossover study, with a 10-day wash-out between study periods. Gabapentin plasma levels were measured for 48 hours following dosing on days 1 and 8.

Figure 1 shows the pharmacokinetic model that described the data adequately.

Figure 1. Schematic of pharmacokinetic model.

Table 5 lists the estimates of mean and inter-subject variability in pharmacokinetic parameters along with residual variability.

Table 5. Final parameter values estimated by the model. %RSE relative standard error; %CV coefficient of variation. ; CI confidence interval.

Parameter	Typical value	%RSE*	95% CI*
Oral clearance (*CL/F*, $L \cdot h^{-1}$)	15.3	5.8%	13.9 – 17.6
Volume of distribution (*Vc/F*, L)	95.4	6.2%	86.7 – 111.0
Inter-compartmental clearance (*Q*, $L \cdot h^{-1}$)	2.39	12.8%	1.93 – 3.11
Peripheral volume (*Vp*, L)	21.4	10.3%	17.7 – 26.5
Absorption rate constant (k_a, h^{-1})	0.56	6. 03%	0.49 – 0.62
Mean transit time (*MTT*, h)	0.696	22.8%	0.407 – 0.980
Number of transit compartments (*N*)	2.71		1.14 – 49.4
Bioavailability of 600 mg G-ER formulation when administered with meal containing 40% calories from fat	1.06	6.38%	0.95 – 1.22
Bioavailability of 600 mg G-ER formulation when administered with meal containing 50% calories from fat	1.35	8.03%	1.16 – 1.60
Bioavailability of 600 mg G-ER formulation when administered with meal containing 30% calories from fat	0.868	8.89%	0.734 – 1.041
Bioavailability of 600 mg G-ER formulation when administered in fasting state	0.633	28.6%	0.544 – 0.890
Decrease in bioavailability from the baseline (600mg dose) with dose increase of 1000 mg, when administered with meal containing 40% calories from fat	0.143	12.1%	0.116 – 0.182
Lag time after administration of gabapentin with food containing 30-40% fat	0.23	5.98%	0.202 - 0.257
Lag time after administration of gabapentin with food containing 50% and in fasting condition	0.16	14.56%	0.13 – 0.22
Tablet release time (h) after administration in a fasting state (*TAU*, h)	0.512	42.12%	0.179 – 1.001
Increase in tablet release time with every 10% increase of fat content (h)	1.19	8.15%	1.01 – 1.38
Interindividual Variability (IIV, variances & %CV)			
Oral clearance ($\eta_{CL/F}$)	0.033 (18.2%)	30.8%	0.056 – 0.182
Apparent volume of distribution ($\eta_{V/F}$)	0.062 (24.8%)	127.5%	0.036 – 0.103

Parameter	Typical value	%RSE*	95% CI*
Absorption rate constant (η_{ka})	0.168 (40.9%)	23.3%	0.092 – 0.241
Inter-compartmental clearance (η_Q) and peripheral volume (η_{Vp})	0.348 (58.9%)	23.1%	0.203 – 0.506
Covariance $\eta_{CL/F} \sim \eta_{V/F}$ (covariance & correlation)	0.027 (0.60)	40.3%	0.056 – 0.166
Interoccasional Variability (IOV, variances & %CV)			
Bioavailability (IOV_F) after administration with food containing 50% fat	0.032 (17.7%)	52.6%	0.007 – 0.069
Increase in IOV in bioavailability after administration of G-ER formulation with fat containing 30-40% fat (k_{F_M})	1.52	38.5%	0.96 – 2.23
Increase in IOV in bioavailability after administration of G-ER formulation in fasting state (k_{F_F})	2.11	56.1	0.06 – 3.23
Tablet release time after G-ER administration with food containing 50% fat (k_{tau_H})	2.58	43.6%	1.62 – 5.78
Tablet release time after G-ER administration with food containing 40% fat (factor times k_{tau_M})	3.2	37.3%	1.99 – 6.33
Tablet release time after G-ER administration with food containing 30% fat (factor times k_{tau_L})	2.26	44.3%	1.09 – 5.08
Tablet release time after G-ER administration in fasting condition (k_{tau_F})	6.11	49.2%	4.11 – 14.72
Residual variability			
Additive error (ε_{add}, $mg \cdot L^{-1}$)	0.0247	8.1%	0.0211– 0.0287
Proportional error (ε_{cv}), disposition phase (> 6h post dosing)	0.0786	7.2%	0.0668- 0.0889
Proportional error in absorption phase (between 2-6h)	0.215	6.9%	0.184 – 0.243
Proportional error in absorption delay phase (< 2h)	0.64	6.9%	0.54 – 0.72
Interindividual variability in residual variability (IIV, variances & %CV)	0.0913 (30.2)	19.7%	0.129 – 0.302

* Assessed by nonparametric bootstrap, n=700

Figure 2 shows the observed, population predicted and individual predicted gabapentin concentrations versus time stratified by study.

Figure 2. Observed, population predicted and individual predicted gabapentin concentrations versus time, stratified by each study. The trend line is shown in red color.

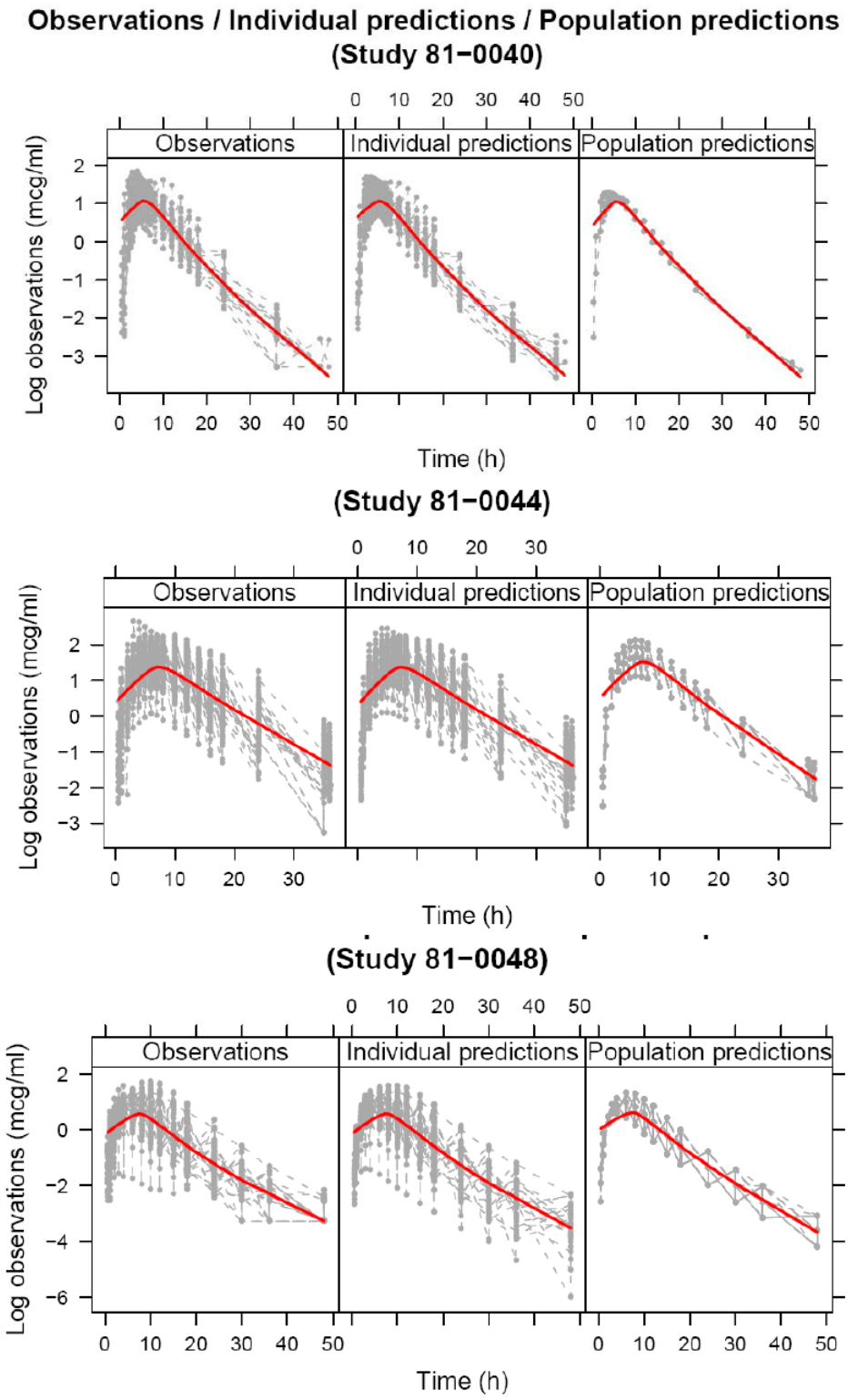


Figure 3 and Figure 4 shows the observed, population predicted and individual predicted concentrations in few subjects.

Figure 3. Observed, population predicted and individual predicted gabapentin concentrations versus time profiles from 15 subjects in Study 81-0040.

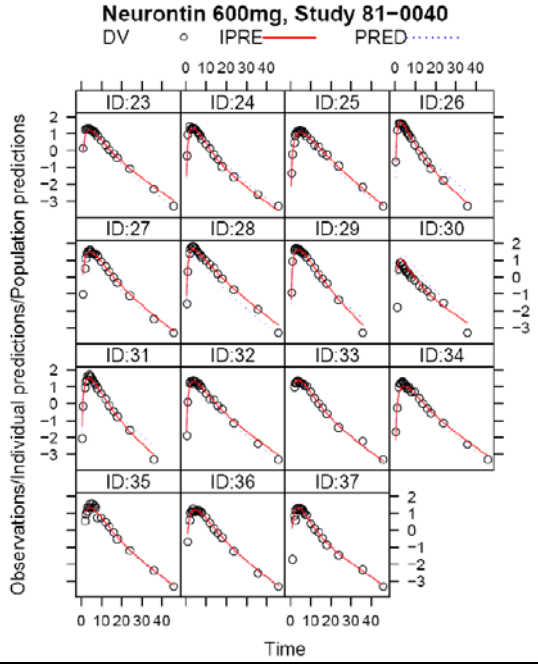
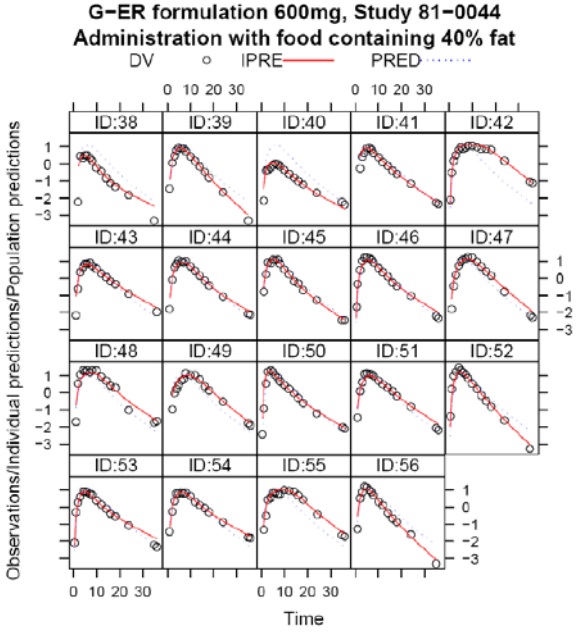


Figure 4. Individual concentration-time profiles from 19 subjects in Study 81-0044.



Reviewer's Comments: The pharmacokinetic analysis conducted by the sponsor is acceptable.

Simulations for deriving dosage recommendations in patients with renal impairment
Simulations were conducted to derive dosing guidelines for patients with varying degrees of renal function in comparison to the efficacious daily dose of 1800 mg G-ER for patients with a renal function as measured by a creatinine clearance value of greater than or equal to 60 mL/min. The proposed doses were selected based on two criteria from simulations:
1. Achievement of average steady state gabapentin concentrations similar to those in the targeted patient population.
2. Cmax and Cmin levels of gabapentin at steady state comparable to those in the targeted patient population.

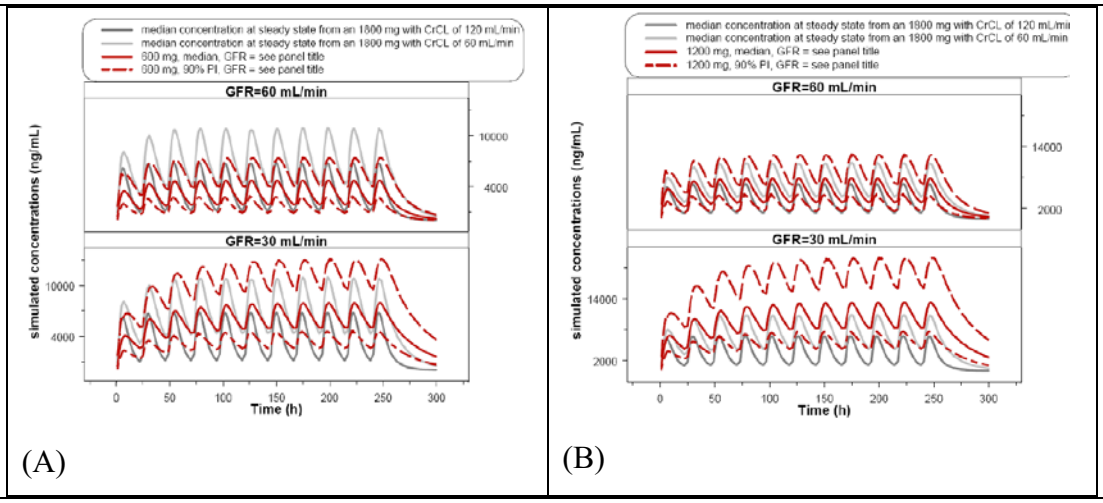
Creatinine Clearance (mL/min) 30-60 mL/min:

The simulated gabapentin concentrations in patients taking G-ER tablets with moderate and high-fat meal are shown Figure 5 and Figure 6 respectively. For comparison purposes, mean simulated gabapentin concentrations in patients with CrCL of 60 and 120 mL/min are also shown.

Creatinine Clearance (mL/min) 15-30 mL/min:

The simulated gabapentin concentrations in patients taking G-ER tablets with moderate and high-fat meal are shown Figure 7 and Figure 8 respectively. For comparison purposes, mean simulated gabapentin concentrations in patients with CrCL of 60 and 120 mL/min are also shown.

Figure 5. Simulated median individual plasma time concentration profiles with 90% prediction intervals for subjects with a creatinine clearance of 30 and 60 mL/min, receiving the recommended dose of (A) 600 mg gabapentin (one 600 mg G-ER tablet) once daily (B) 1200 mg gabapentin (two 600 mg G-ER) with a moderate-fat meal (500-600 calories, 40% from fat). Simulated median plasma concentration-time profiles for a subject with a creatinine clearance of 60 and 120 mL/min administered an 1800 mg gabapentin (three 600 mg G-ER tablets) once daily are shown for comparison.

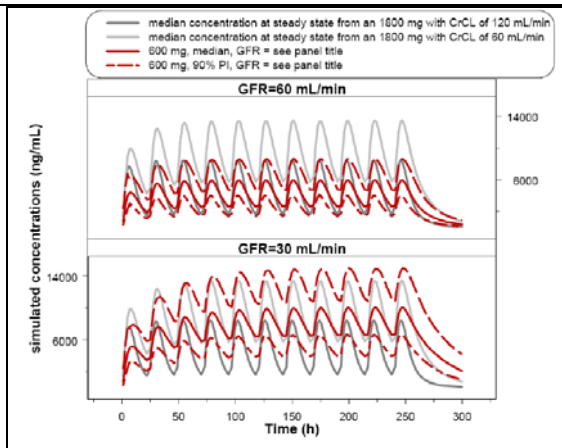


Reviewer's Comments:

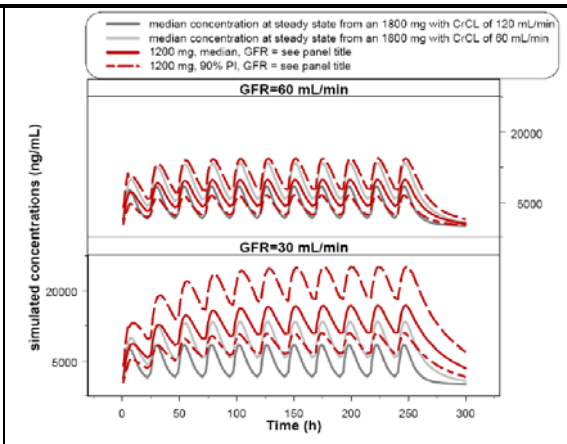
Simulations after administration of G-ER with moderate-fat meal indicate that

- The median concentrations after 1200 mg dose in patients with CrCL of 60 mL/min is within the range of concentrations after 1800 mg dose in patients with CrCL of 60-120 mL/min.
- The median concentrations after 600 mg dose in patients with CrCL of 30 mL/min is within the range of concentrations after 1800 mg dose in patients with CrCL of 60-120 mL/min.

Figure 6. Simulated median individual plasma time concentration profiles with 90% prediction intervals for subjects with a creatinine clearance of 30 and 60 mL/min, receiving the recommended dose of (A) 600 mg gabapentin (one 600 mg G-ER tablet) once daily (B) 1200 mg gabapentin (two 600 mg G-ER) with a high-fat meal (900-1000 calories, 50% from fat). Simulated median plasma concentration-time profiles for a subject with a creatinine clearance of 60 and 120 mL/min administered an 1800 mg gabapentin (three 600 mg G-ER tablets) once daily are shown for comparison.



(A)

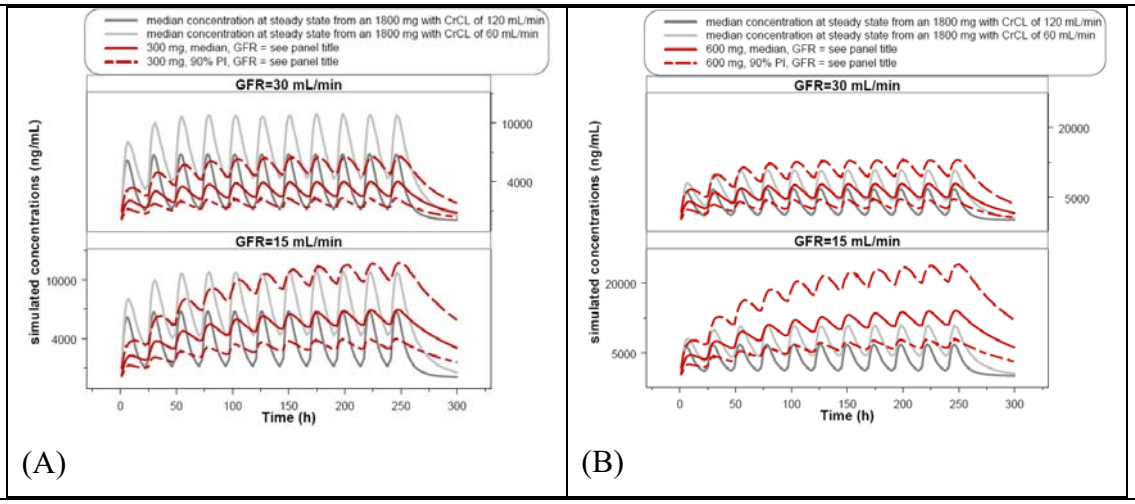


(B)

Simulations after administration of G-ER with high-fat meal indicate that

- The median concentrations after 1200 mg dose in patients with CrCL of 60 mL/min is within the range of concentrations after 1800 mg dose in patients with CrCL of 60-120 mL/min.
- The median concentrations after 600 mg dose in patients with CrCL of 30 mL/min is within the range of concentrations after 1800 mg dose in patients with CrCL of 60-120 mL/min.

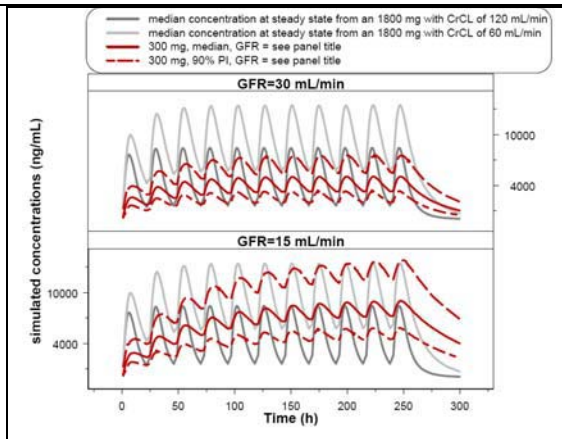
Figure 7. Simulated median individual plasma time concentration profiles with 90% prediction intervals for subjects with a creatinine clearance of 15 and 30 mL/min, receiving the recommended dose of (A) 300 mg gabapentin (one 300 mg G-ER tablet) once daily (B) 600 mg gabapentin (one 600 mg G-ER) with a moderate-fat meal (500-600 calories, 40% from fat). Simulated median plasma concentration-time profiles for a subject with a creatinine clearance of 60 and 120 mL/min administered an 1800 mg gabapentin (three 600 mg G-ER tablets) once daily are shown for comparison.



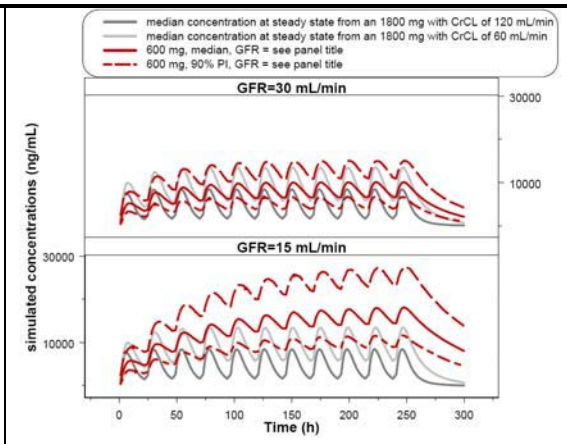
Simulations after administration of G-ER with moderate-fat meal indicate that

- The median concentrations after 600 mg dose in patients with CrCL of 30 mL/min is within the range of concentrations after 1800 mg dose in patients with CrCL of 60-120 mL/min.
- The median concentrations after 300 mg dose in patients with CrCL of 15 mL/min is within the range of concentrations after 1800 mg dose in patients with CrCL of 60-120 mL/min.

Figure 8. Simulated median individual plasma time concentration profiles with 90% prediction intervals for subjects with a creatinine clearance of 15 and 30 mL/min, receiving the recommended dose of (A) 300 mg gabapentin (one 300 mg G-ER tablet) once daily (B) 600 mg gabapentin (one 600 mg G-ER) with a high-fat meal (900-1000 calories, 50% from fat). Simulated median plasma concentration-time profiles for a subject with a creatinine clearance of 60 and 120 mL/min administered an 1800 mg gabapentin (three 600 mg G-ER tablets) once daily are shown for comparison.



(A)



(B)

Simulations after administration of G-ER with high-fat meal indicate that

- The median concentrations after 600 mg dose in patients with CrCL of 30 mL/min is within the range of concentrations after 1800 mg dose in patients with CrCL of 60-120 mL/min.
- The median concentrations after 300 mg dose in patients with CrCL of 15 mL/min is within the range of concentrations after 1800 mg dose in patients with CrCL of 60-120 mL/min.

Reviewer's Comments:

Based on the simulations the sponsor's proposed adjustments to G-ER dose are

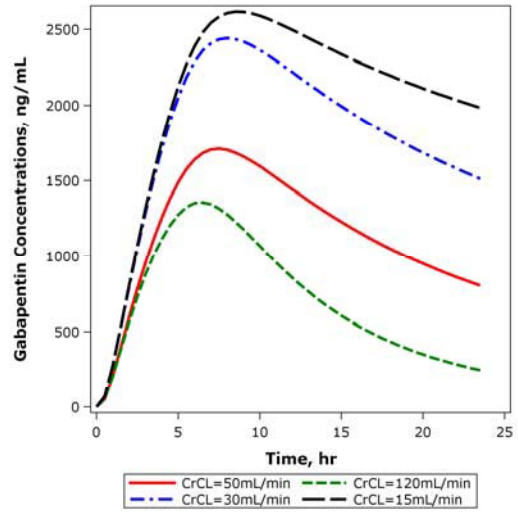
- 600-1800 mg in patients with creatinine clearance of 30-60 mL/min.
- (b) (4)

Figure 9 shows the simulated time course of gabapentin concentrations in patients with various degrees of renal function after first dose and at steady state based on proposed dosing guidelines. Simulations suggest that the concentrations of gabapentin will be higher initially, based on proposed dosing guidelines, in patients with creatinine clearance of 15-30 mL/min relative to those with creatinine clearance of 50 and 120 mL/min. It is possible that the higher initial concentrations of gabapentin could lead to

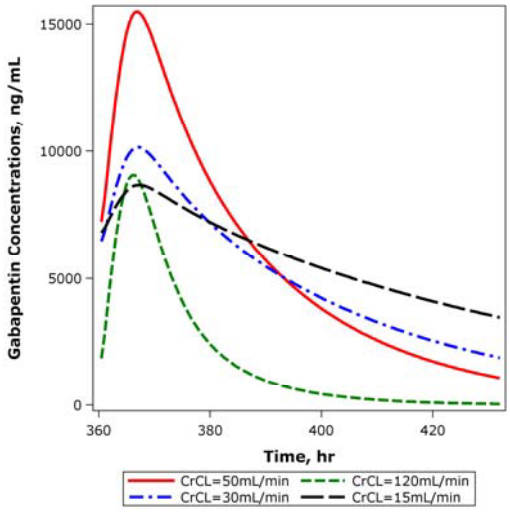
tolerability issues. Based on simulations, the proposed dosing guidelines for G-ER formulation are:

Renal Function Creatinine Clearance (mL/min)	G-ER dose, mg (Once-daily with evening meal)
≥60	1800
30-60	600 to 1800
15-30	Should not be administered

Figure 9. Simulated gabapentin concentrations after administration of G-ER doses based on creatinine clearance.



First Dose



Steady State

For patients with CrCL 50 and 120 mL/min, simulations are conducted based on titration scheme as shown in Table 1. In patients with CrCL 15 mL/min, the starting dose and final dose is 300 mg with no titration. In patients with CrCL 30mLmin, the starting dose is 300 mg with maintanence dose of 600 mg from Day2.

4 REVIEWER'S ANALYSIS

NA

4.1 Introduction

NA

4.2 Objectives

NA

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 6.

Table 6. Analysis Data Sets

Study Number	Name	Link to EDR

4.3.2 Software

Specify the software used for the analysis.

4.3.3 Models

4.4 Results

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\

4.3 Individual Study Synopses:

Note: Study synopses in this section were extracted from the NDA submission

4.3.1 Study Designs:

Clinical Pharmacology Studies:

Study 81-0008*: Comparison of Gabapentin Pharmacokinetics for Gastric Retentive (GR) Tablets Versus Immediate Release (lR) Capsules in Healthy Volunteers.*

Study 81-0040: *A Four-Way Crossover, Open-Label, Single-Dose, Fed, Dosage Form Proportionality Comparison Study of Gabapentin Extended Release 600 mg Tablets Versus Two Formulations of Gabapentin Extended Release 300 mg Tablets and Neurontin® 600 mg Tablets in Normal Healthy Non-Smoking Male and Female Subjects*

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Study 81-0044: *A Four-Arm, Non-Randomized, Open-Label, Single-Dose, Fed, Comparative Bioavailability Study of Escalating Doses of Gabapentin Extended Release Tablets, 600 mg in Healthy, Non-Smoking Male Subjects*

Study 81-0048: *A Three-Way Crossover, Open-Label, Single-Dose, Food-Effect, Relative Bioavailability Study of Gabapentin Extended-Release 600 mg Tablets in Normal, Healthy, Non-Smoking Male and Female Subjects*

Study 81-0049: *A Three-Way Crossover, Open-Label, Fed Study Comparing the Pharmacokinetic Prof'Iles of Gabapentin Extended Release Tablets Versus Neurontin® Immediate Release Tablets on Day 1 and After 5 Days of Multiple Administration in Normal, Healthy, Non-Smoking Male and Female Subjects*

Study 81-0050: *A Four-Way Crossover, Open-Label, Single-Dose, Fed, Pharmacokinetic Study Of 3 Formulations Of Gabapentin Extended Release (ER) Tablets And Neurontin® Immediate Release 600 mg Tablets In Healthy, Non-Smoking Male And Female Subjects For Investigation Of In-Vitro/In-Vivo Correlation.*

Study Reports 85-0009 and 85-0010*: Modeling and simulation for G-ER dosing in renally impaired patients using gabapentin plasma concentration data from 3 pharmacokinetic studies*

4.3.2 Study Synopses

Study 81-0008:

Name of Sponsor/Company: DepoMed, Inc	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: Test Drugs: Gabapentin GR6 Tablets, 300 mg Gabapentin GR8 Tablets, 300 mg Gabapentin GR8 Tablets, 600 mg Reference Drug: Neurontin® capsules 300 mg		
Name of Active Ingredient: Gabapentin		

Title of Study:
Comparison of Gabapentin Pharmacokinetics for Gastric Retentive (GR) Tablets Versus Immediate Release (IR) Capsules in Healthy Volunteers.

Investigator:
"Leiter der klinischen Prüfung" according to § 40 German Drug Law (Principal Investigator):
Dr. med. Margarete Müller

For a list and description of sub-investigators and other important participants in the study, including their role in the study and brief CVs please refer to 16.1.4.

Study Centre:
AAI Deutschland GmbH & Co KG
Wegenerstraße 13
89231 Neu-Ulm
Germany

Publication (reference):
Not applicable.

Studied period:	Phase of development:
Date of first enrolment: 05.11.2001 Date of last completed: 19.12.2001	Phase I

Objectives:
The primary objectives of this study were as follows:
- To demonstrate extended delivery of gabapentin from GR tablets in plasma concentration-time and urinary excretion rate-time profiles of gabapentin.
- To compare the extent of absorption (excretion) of gabapentin from GR tablets versus gabapentin IR capsules.

Methodology:
Open-label, randomized, four-way crossover design

Number of subjects (planned and analysed):
Number of subjects planned for enrollment: 16
Subjects enrolled: 16
Minimum number of subjects planned to complete: 12
Number of subjects completing period 1, 2 and analysed: 16
Number of subjects completing period 3, 4 and analysed: 15 (subject # 6 dropped out)

Diagnosis and main criteria for inclusion:
Healthy male or female volunteers, 18 to 50 years of age, with normal gastrointestinal function.

Investigational Product 1, dose and mode of administration, batch number:
Gabapentin GR6 Tablets, 300 mg (containing 300 mg gabapentin), tablet for oral administration, batch number: 010100
Investigational Product 2, dose and mode of administration, batch number:
Gabapentin GR8 Tablets, 300 mg (containing 300 mg gabapentin), tablet for oral administration, batch number: 010101
Investigational Product 3, dose and mode of administration, batch number:
Gabapentin GR8 Tablets, 600 mg (containing 600 mg gabapentin), tablet for oral administration, batch number: 010102

Reference drug, dose and mode of administration, batch number:
Neurontin® (containing 300 mg gabapentin), capsules for oral administration, batch number: 17381V

Duration of treatment:
Four (4) times single dose.

Study 81-0008:

Name of Sponsor/Company: DepoMed, Inc	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Test Drugs: Gabapentin GR6 Tablets, 300 mg; Gabapentin GR8 Tablets, 300 mg; Gabapentin GR8 Tablets, 600 mg; Reference Drug: Neurontin® capsules 300 mg	Volume:	
Name of Active Ingredient: Gabapentin	Page:	

Criteria for evaluation:

Efficacy:	Not applicable.
Pharmacodynamics:	Not applicable.
Pharmacokinetics:	C_{max}, t_{max}, AUC(0-24), AUC(0-∞) and $t_{1/2}$; Ae, R_{max} and CL_R. The relative bioavailability of gabapentin from GR6 tablets, 300mg, GR8 Tablets, 300 mg and GR8 Tablets, 600 mg was determined based on AUC comparisons with IR gabapentin capsules.
Safety:	Adverse events, blood pressure, pulse, oral temperature, clinical laboratory, physical examination and ECG.

Statistical methods:
Analysis of variance of AUC, C_{max} and Ae with sequence, subject within sequence, period and treatment effects, for AUC and C_{max} after logarithmic pre-transformation. Pairwise nonparametric comparisons of t_{max}.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:
Not applicable.

PHARMACODYNAMIC RESULTS:
Not applicable.

PHARMACOKINETIC RESULTS:
All three GR tablets exhibited sustained-release properties. The maximal concentration C_{max} was reduced by about 35% and t_{max} increased by between 1 and 1.5 hours, most so for the 600mg preparation (treatment D). The half-life was not affected.
All three test products were found to differ significantly from the reference product with respect to C_{max} and t_{max}, but not with respect to AUC(0-24) or AUC(0-∞).
The GR tablets did not differ statistically from Neurontin® with respect to the total urinary recovery within 48 hours (Ae). In the median, Ae corresponded to a recovery of about 50% of the administered dose.

SAFETY RESULTS:
All four treatments were tolerated well. No serious adverse events were reported and none of the subjects withdrew due to an adverse event. The frequency of adverse events was low. Fifteen (15) subjects reported adverse events, i.e. 3 subjects after treatment A, 2 subjects after treatment B and 5 subjects after treatment C and D, respectively. In total, 28 post-dose adverse events were reported, 12 of them were considered to be possibly drug related. Most of the adverse events were mild in intensity. The following drug-related adverse events were observed:
Treatment A: tiredness and headache (2 episodes in 1 subject).
Treatment B: irritation of the throat with retching (1 episode).
Treatment C: diarrhoea (2 episodes in 2 subjects), vomiting (2 episodes in 2 subjects), gastric disorder (1 episode), feeling of pressure in the stomach (1 episode), nose bleeding (1 episode).
Treatment D: gastric disorder and pasty stool (2 episodes in 1 subject).
For laboratory tests, only single values outside the reference ranges were observed without obvious trend or pattern.
Mean blood pressure, pulse and body temperature remained stable after dosing of all four treatments.

CONCLUSION:
All three GR products demonstrated statistically significant lower values for C_{max}, statistically increased values for t_{max} but the AUC- and Ae-values were not statistically different from Neurontin® 300 mg capsules.
GR6 and GR8 tablets of 300 mg did not show any definite differences in their pharmacokinetic profiles.
There were no indications of any clinically relevant difference of the four formulations of gabapentin, with respect to the safety, when administered as an oral single dose of 600 mg.

Date of the report: 12 June 2002

Study 81-0040:

2. SYNOPSIS

Name of Sponsor Company: DEPOMED, INC.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended Release 300 mg Tablets (Lot # 1079) Gabapentin Extended Release 300 mg Tablets (Lot # 1090) Gabapentin Extended Release 600mg Tablets (Lot # 1082)		
Name of Active Ingredient: gabapentin		
Title of Study: **A Four-Way Crossover, Open-Label, Single-Dose, Fed, Dosage Form Proportionality Comparison Study of Gabapentin Extended Release 600 mg Tablets Versus Two Formulations of Gabapentin Extended Release 300 mg Tablets and Neurontin® 600 mg Tablets in Normal Healthy Non-Smoking Male and Female Subjects** **Protocol No.: 3022**		
Investigators: Principal Investigator: Paul Y. Tam, M.D., F.R.C.P, F.A.C.P. Sub-investigator: (b) (4)		
Study Center: Biovail Contract Research - 460 Comstock Road, Toronto, ON, M1L 4S4 Canada - 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada		
Publications based on this study: None		
Study Period: May 16, 2005 to June 9, 2005	*Phase of Development:* Phase I, dosage form proportionality comparison	

Study 81-0040:

Name of Sponsor Company: DEPOMED, INC.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended Release 300 mg Tablets (Lot # 1079) Gabapentin Extended Release 300 mg Tablets (Lot # 1090) Gabapentin Extended Release 600mg Tablets (Lot # 1082)		
Name of Active Ingredient: gabapentin		

Objectives:

The primary objective of this study was to evaluate the dosage form proportionality of gabapentin following administration of three formulations of Gabapentin Extended Release: Gabapentin Extended Release 600mg Tablets (Lot # 1082), Gabapentin Extended Release 300mg Tablets (Lot # 1079), Gabapentin Extended Release 300mg Tablets (Lot # 1090), under fed conditions.

The secondary objectives of this study were:

- To generate pharmacokinetic data to design the *in-vitro/in-vivo* correlation (IVIVC) of gabapentin from three different formulations of Gabapentin Extended Release and Neurontin® 600mg (immediate release) Tablets.
- To evaluate the safety of three formulations of Gabapentin Extended Release and Neurontin® Immediate Release following single dose administration.

Main Criteria for Inclusion:
Normal, healthy, non-smoking male and female subjects within an age range of 18 to 50 years.

Test Products/Investigational Products, Lot Numbers and Mode of Administration:
The following four test products were administered as treatments: 1 Gabapentin Extended Release 600mg Tablet (Lot #: 1082), 2 Gabapentin Extended Release 300 mg Tablets (Lot # 1079), 2 Gabapentin Extended Release 300 mg Tablets (Lot # 1090), and 1 Neurontin® 600mg (immediate release) Tablet (Lot # 28144V). (Treatment dose = 600 mg)

Mode of Administration:
Following an overnight fast of at least 10 hours, and 20 minutes after the start of a standardized, approximately 500-600 calorie, moderate-fat (approximately 40%) content meal, the specified treatment to which the subject was randomized for that study period was administered orally with 180 mL of ambient temperature water. (Treatment dose = 600 mg)

Study 81-0040:

Name of Sponsor Company: DEPOMED, INC.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended Release 300 mg Tablets (Lot # 1079) Gabapentin Extended Release 300 mg Tablets (Lot # 1090) Gabapentin Extended Release 600mg Tablets (Lot # 1082)		
Name of Active Ingredient: gabapentin		

Treatment Periods:

Period I: May 17, 2005
Period II: May 24, 2005
Period III: May 31, 2005
Period IV: June 7, 2005

Number of Subjects (planned and analyzed):

There were 16 subjects dosed in Period I, 15 of whom completed the study. One subject was dismissed for administrative reasons. Pharmacokinetic and statistical analyses were performed on the 15 subjects who completed the study.

Blood Draw Timepoints:

During each study period, 24 blood samples were collected from each subject at the following timepoints: 0.0 (pre-dose), 0.5, 1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 24.0, 36.0, 46.0, and 48.0 hours post-dose.

Analytical Procedure:

(b) (4)

Study 81-0040:

Name of Sponsor Company: DEPOMED, INC.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended Release 300 mg Tablets (Lot # 1079) Gabapentin Extended Release 300 mg Tablets (Lot # 1090) Gabapentin Extended Release 600mg Tablets (Lot # 1082)		
Name of Active Ingredient: gabapentin		

Criteria for Evaluation:

The pharmacokinetic analysis was performed on 15 subjects who completed the four study periods. The safety assessment was performed on all subjects who received at least one dose during the course of the study.

Pharmacokinetics (PK):

The following pharmacokinetic parameters for gabapentin were calculated by standard non-compartmental methods: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and $t_{½}$.

Safety:

The incidences of all adverse events (AEs) were tabulated by treatment and subject number. Absolute values for laboratory parameters were documented and values outside their respective normal ranges were flagged. Absolute values for vital signs, electrocardiogram (ECG) parameters, and physical examinations were also documented and values outside the normal range were flagged. Shifts from baseline values were tabulated. AEs were documented using investigator and Medical Dictionary for Regulatory Activities (MedDRA) terms.

Statistical Methods:

Using General Linear Model (GLM) procedures in Statistical Analysis System (SAS), analysis of variance (ANOVA) was performed on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} and on untransformed $t_{½}$ at the significance level of 0.05. The intra-subject coefficient of variation (CV) was calculated using the Mean Square Error (MSE) from the ANOVA table. The ratio of geometric means and the 90% geometric confidence interval (90% C.I.) were calculated based on the difference in the Least Squares Means of the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} between the test and reference formulations. T_{max} was analyzed using nonparametric methods.

Summary of Safety Results:

No serious adverse events were reported. No subjects discontinued prematurely due to AEs.

There were a total of seven AEs reported by six subjects during the study. Five AEs were "possibly" related to the study drug. All subjects who experienced AEs during this study recovered completely. No significant safety concerns emerged.

Study 81-0040:

Name of Sponsor Company: DEPOMED, INC.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended Release 300 mg Tablets (Lot # 1079) Gabapentin Extended Release 300 mg Tablets (Lot # 1090) Gabapentin Extended Release 600mg Tablets (Lot # 1082)		
Name of Active Ingredient: gabapentin		

Summary of Pharmacokinetic Results:

PHARMACOKINETIC PARAMETERS FOR GABAPENTIN:

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD			
	Gabapentin Extended Release 1 x 600mg Tablets (Lot #1082) (A) (n=15)	Gabapentin Extended Release 2 x 300 mg Tablets (Lot # 1079) (B) (n=15)	Gabapentin Extended Release 2 x 300 mg Tablets (Lot # 1090) (C) (n=15)	Neurontin® 1 x 600mg (immediate release) Tablets (D) (n=15)
AUC_{0-t} (ng·hr/mL)	37608 (32) 39315 ± 12432	39710 (33) 41921 ± 13852.	34883 (41) 37456 ± 15243	40433 (22) 41519 ± 9006
AUC_{0-inf} (ng·hr/mL)	38911 (30) 40515 ± 12264	41115 (31) 43172 ± 13576	36085 (39) 38573 ± 15182	41727 (21) 42694 ± 8857
C_{max} (ng/mL)	3257 (26) 3362 ± 890	3314 (26) 3416 ± 879	2845 (35) 2982 ± 1054	4243 (24) 4367 ± 1054
T_{max} (hr)*	6.00 (3.00 - 10.00)	6.50 (4.50 - 10.03)	5.00 (3.50 - 10.00)	3.50 (2.00 – 5.00)
$t_{1/2}$ (hr)	6.61 ± 1.62	6.72 ± 1.78	6.67 ± 1.95	6.46 ± 1.26

* median (min – max)

BIOEQUIVALENCE ASSESSMENTS FOR GABAPENTIN (TREATMENT B VERSUS TREATMENT A):

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	90.50% to 122.59%	105.33%	24.98%
AUC_{0-inf}	91.44% to 121.60%	105.45%	23.43%
C_{max}	92.18% to 111.98%	101.60%	15.88%

Study 81-0040:

Name of Sponsor Company: DEPOMED, INC.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended Release 300 mg Tablets (Lot # 1079) Gabapentin Extended Release 300 mg Tablets (Lot # 1090) Gabapentin Extended Release 600mg Tablets (Lot # 1082)		
Name of Active Ingredient: gabapentin		

BIOEQUIVALENCE ASSESSMENTS FOR GABAPENTIN (TREATMENT C VERSUS TREATMENT A):

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	79.00% to 107.01%	91.94%	24.98%
AUC_{0-inf}	79.81% to 106.13%	92.03%	23.43%
C_{max}	79.14% to 96.14%	87.23%	15.88%

Conclusion:

The objective of this study was to evaluate the dosage form proportionality of 3 formulations of Gabapentin Extended Release (ER) under fed conditions to aid in the selection of two dosage strengths that are dosage form proportional. The bioavailability of gabapentin was assessed by measuring the peak and total systemic exposure from the four treatments (using AUC_{0-t}, AUC_{0-inf}, and C_{max}). On comparing treatments B vs. A, the statistical results indicated that the 90% confidence interval of the geometric mean ratio for C_{max}, AUC_{0-t} and AUC_{0-inf} were within the 80-125% acceptance criteria. In contrast, on comparing treatments C vs. A, the statistical results indicated that the 90% confidence intervals of the geometric mean ratio for C_{max}, AUC_{0-t} and AUC_{0-inf} did not meet the 80-125% acceptance criteria. Treatments A and B, but not A and C, meet the requirements of dosage form proportionality. The pharmacokinetics of the reference Neurontin® 600 mg tablets were also evaluated to design the *in vivo-in/vitro* correlation.

No SAEs were reported. No subjects discontinued prematurely due to AEs. All subjects who experienced AEs during this study recovered completely.

Overall, Gabapentin Extended Release Tablets were well tolerated as a single-dose of 2 x 300 mg and 1 x 600 mg, administered under fed conditions, and no significant safety issues emerged.

Report Issue Date:
November 18, 2005

This study was performed in compliance with GCP.

Study 81-0044:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended Release Tablets, 600 mg		
Name of Active Ingredient: gabapentin		
Title of Study: **A Four-Arm, Non-Randomized, Open-Label, Single-Dose, Fed, Comparative Bioavailability Study of Escalating Doses of Gabapentin Extended Release Tablets, 600 mg in Healthy, Non-Smoking Male Subjects** **Protocol No.: 3160 (81-0044)**		
Investigators: Principal Investigator: Paul Y. Tam, M.D., F.R.C.P, F.A.C.P. Sub-investigators: (b) (4)		
Study Center: Biovail Contract Research - 460 Comstock Road, Toronto, ON, M1L 4S4 Canada - 689 Warden Avenue, Units 1 & 2, Toronto, ON, M1L 4R6 Canada		
Publications based on this study: None		
Study Period: September 17, 2005 to October 11, 2005	*Phase of Development:* Phase I	
Objectives: The objective of this study was to compare the rate and extent of absorption of gabapentin following administration of four escalating doses of a test formulation of Gabapentin Extended Release Tablets, 600 mg under fed conditions. The secondary objective of this study was to evaluate the tolerability and safety of the four doses of a test formulation of Gabapentin Extended Release Tablets, 600 mg following single dose administration.		
Main Criteria for Inclusion: Normal, healthy, non-smoking male subjects between the ages of 18 and 65 years.		

Study 81-0044:

Name of Sponsor Company: Depomed, Inc. *Name of Finished Product:* Gabapentin Extended Release Tablets, 600 mg *Name of Active Ingredient:* gabapentin	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***

Test Product/Investigational Product, Batch or Lot Number and Mode of Administration:

Treatment A (Period I): Following an overnight fast of at least 10 hours, and 20 minutes after the start of a standardized, approximately 500-600 calorie, moderate fat (~40%) content meal, 1 Gabapentin Extended Release Tablet, 600 mg, Lot #: 1082, administered orally with 240 mL of ambient temperature water (Treatment Dose = 600 mg).

Treatment B (Period II): Following an overnight fast of at least 10 hours, and 20 minutes after the start of a standardized, approximately 500-600 calorie, moderate fat (~40%) content meal, 2 Gabapentin Extended Release Tablets, 600 mg, Lot #: 1082, administered orally with 240 mL of ambient temperature water (Treatment Dose = 1200 mg).

Treatment C (Period III): Following an overnight fast of at least 10 hours, and 20 minutes after the start of a standardized, approximately 500-600 calorie, moderate fat (~40%) content meal, 3 Gabapentin Extended Release Tablets, 600 mg, Lot #: 1082, administered orally with 240 mL of ambient temperature water (Treatment Dose = 1800 mg).

Treatment D (Period III): Following an overnight fast of at least 10 hours, and 20 minutes after the start of a standardized, approximately 500-600 calorie, moderate fat (~40%) content meal, 4 Gabapentin Extended Release Tablets, 600 mg, Lot #: 1082, administered orally with 240 mL of ambient temperature water (Treatment Dose = 2400 mg).

Treatment Periods:

Period I:	September 18, 2005
Period II:	September 25, 2005
Period III:	October 3, 2005
Period IV:	October 10, 2005

Number of Subjects (planned and analyzed):

There were 24 subjects dosed in Period I, 19 of whom completed the study. One subject was dismissed due to AEs and use of concomitant medication. Two subjects were dismissed due to administrative reasons and 2 subjects withdrew for personal reasons. Pharmacokinetic and statistical analyses were performed on the 19 subjects who completed the study.

Study 81-0044:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only***: Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended Release Tablets, 600 mg		
Name of Active Ingredient: gabapentin		

Blood Draw Timepoints:
During each study period, 18 blood samples were collected from each subject at the following timepoints: 0.0 (pre-dose), 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 24.0, 35.0, and 36.0 hours post-dose.

Analytical Procedure:

(b) (4)

[redacted]

Criteria for Evaluation:
The pharmacokinetic analysis was performed on 19 subjects who completed the 4 study periods. The safety assessment was performed on all subjects who received at least 1 dose during the course of the study.

Pharmacokinetics (PK):
The following pharmacokinetic parameters for gabapentin were calculated by standard non-compartmental methods: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el}, and $t_{½}$.

Safety:
The incidences of all adverse events (AEs) were tabulated by treatment and subject number. Absolute values for laboratory parameters were documented and values outside their respective normal ranges were flagged. Absolute values for vital signs, electrocardiogram (ECG) parameters, laboratory parameters and physical examinations were also documented and values outside the normal range were flagged. Shifts from baseline values were tabulated. AEs were documented using investigator and Medical Dictionary for Regulatory Activities (MedDRA) terms.

Study 81-0044:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended Release Tablets, 600 mg		
Name of Active Ingredient: gabapentin		

Statistical Methods:

Parameters were listed for all subjects and summarized for each gabapentin dose by means of descriptive statistics. The natural log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were used for data analysis.

The secondary variables, T_{max} and $t_{1/2}$, were not log-transformed and were summarized for each gabapentin dose.

The ln-transformed parameters AUC_{0-t}, AUC_{0-inf} and C_{max} (after dose normalization) were analyzed by ANOVA. Estimates of the pair-wise ratios between each dose and reference dose (600 mg) were calculated together with 90% CIs. The 90% CI was used to assess dose proportionality; i.e. the CI of the ratio should contain 100% and possibly lie within 80-125%.

Summary of Safety Results:

No serious adverse events were reported. One subject was discontinued prematurely due to AEs and use of concomitant medication.

There were a total of 28 AEs reported by 9 subjects during the study. No AE occurred in 20% or more of the subjects, after administration of Gabapentin Extended Release Tablets, 600 mg. Twenty-three AEs were "possibly" related to the study drug. All subjects who experienced AEs during this study recovered completely. No significant safety concerns emerged.

Study 81-0044:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended Release Tablets, 600 mg	*Page:*	
Name of Active Ingredient: gabapentin		

Summary of Pharmacokinetic Results:

PHARMACOKINETIC PARAMETERS FOR GABAPENTIN (WITHOUT DOSE-NORMALIZED DATA):

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD			
	Gabapentin Extended Release Tablets, 1 x 600 mg (A) (n=19)	Gabapentin Extended Release Tablets, 2 x 600 mg (B) (n=19)	Gabapentin Extended Release Tablets, 3 x 600 mg (C) (n=19)	Gabapentin Extended Release Tablets, 4 x 600 mg (D) (n=19)
AUC_{0-t} (ng·hr/mL)	34263.60 (32.23) 36246.60 ± 11682.88	60552.43 (33.50) 63765.17 ± 21361.11	86847.57 (31.97) 91160.00 ± 29143.87	103753.42 (29.52) 108677.75 ± 32080.21
AUC_{0-inf} (ng·hr/mL)	35697.57 (31.66) 37624.33 ± 11910.02	63208.92 (32.85) 66382.89 ± 21805.83	90893.50 (31.27) 95147.22 ± 29755.33	108571.95 (28.59) 113333.68 ± 32397.18
C_{max} (ng/mL)	2840.29 (26.16) 2961.96 ± 774.76	4826.00 (21.31) 4932.55 ± 1051.21	6477.53 (26.14) 6685.59 ± 1747.58	7598.47 (26.79) 7847.06 ± 2102.04
T_{max} (hr)*	6.00 (4.00 - 10.00)	6.00 (3.00 - 12.00)	6.00 (4.00 - 12.00)	7.00 (3.00 - 10.00)
$t_{1/2}$ (hr)	6.43 ± 1.30	6.74 ± 1.19	7.18 ± 1.55	7.32 ± 1.60
K_{el} (hr^{-1})	1.12E-01 ± 2.13E-02	1.06E-01 ± 1.73E-02	1.01E-01 ± 2.45E-02	9.90E-02 ± 2.16E-02

* median (min – max)

Study 81-0044:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only***: Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended Release Tablets, 600 mg		
Name of Active Ingredient: gabapentin		

Conclusion:

The objective of this study was to assess the dose proportionality of gabapentin by comparing the rate and extent of absorption of gabapentin following administration of four escalating doses of a test formulation of Gabapentin Extended Release Tablets, 600 mg under fed conditions.

The dose proportionality was assessed by measuring and comparing the peak and total systemic exposure of gabapentin from the 4 treatment groups (using dose-normalised AUC_{0-t}, AUC_{0-inf}, and C_{max}).

The statistical results indicated that, upon comparing the dose-normalised AUC_{0-t}, AUC_{0-inf}, and C_{max} of the 1200 mg dose of Gabapentin ER tablets to that of the 600 mg dose of Gabapentin ER tablets, the peak and total systemic exposure of gabapentin was similar between the 2 treatments. Upon evaluating the dose-normalised AUC_{0-t}, AUC_{0-inf}, and C_{max} of 1800 mg dose of Gabapentin ER tablets to that of 600 mg dose of Gabapentin ER tablets, the total systemic exposure was similar, but the peak exposure of the 1800 mg dose was significantly lower under the fed conditions. However, the dose-normalised peak and total systemic exposure of the 2400 mg dose of Gabapentin ER tablets was significantly lower than that of the 600 mg dose of Gabapentin ER tablets under fed conditions.

Based on pharmacokinetics of gabapentin, the test formulation of Gabapentin Extended Release Tablets, 600 mg demonstrates dose proportionality between the doses of 600 mg and 1200 mg. However, doses of 1800 mg and 2400 mg failed to exhibit dose proportionality for Gabapentin ER 600 mg tablet under fed administration conditions.

No SAEs were reported. One subject was discontinued prematurely due to AEs and use of concomitant medication. All subjects who experienced AEs during this study recovered completely. Overall, Gabapentin Extended Release Tablets, 600 mg were well tolerated as a single-dose of 600 mg, 1200 mg, 1800 mg and 2400 mg, administered under fed conditions, and no significant safety issues emerged.

Report Issue Date:
March 14, 2005

This study was performed in compliance with GCP.

Study 81-0048:

Name of Sponsor Company: Depomed, Inc. *Name of Finished Product:* Gabapentin Extended-Release Tablets, 600 mg *Name of Active Ingredient:* gabapentin	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***

Title of Study:
A Three-Way Crossover, Open-Label, Single-Dose, Food-Effect, Relative Bioavailability Study of Gabapentin Extended-Release 600 mg Tablets in Normal, Healthy, Non-Smoking Male and Female Subjects

Protocol No.: 3232 (81-0048)

Investigators:
Principal Investigator: Paul Y. Tam, M.D., F.R.C.P, F.A.C.P.

Sub-investigators: (b) (4)

Study Center:
Biovail Contract Research
- 460 Comstock Road, Toronto, ON, M1L 4S4 Canada
- 689 Warden Avenue, Unit 1, Toronto, ON, M1L 4R6 Canada

Publications based on this study:
None

Study Period:	*Phase of Development:*
June 6, 2006 to June 23, 2006	Phase I (bioavailability)

Objectives:
The objective of this study was to evaluate the effect of food on the rate and extent of absorption of gabapentin from a novel formulation of Gabapentin Extended-Release Tablets, 600 mg.

Main Criteria for Inclusion:
Normal, healthy, non-smoking male and female subjects between the ages of 18 and 65 years.

Study 81-0048:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended-Release Tablets, 600 mg	*Page:*	
Name of Active Ingredient: gabapentin		

Test Product/Investigational Product, Lot Number and Mode of Administration:

Treatment A: Following an overnight fast of at least 10 hours, 1 Gabapentin Extended-Release Tablet, 600 mg, Lot #: 06T4221, with 240 mL of ambient temperature water.

Treatment B: Following an overnight fast of at least 10 hours, 1 Gabapentin Extended-Release Tablet, 600 mg, Lot #: 06T4221, with 240 mL of ambient temperature water, 30 minutes after the start of a standardized meal (945 calories and more than 50% of calories from fat).

Treatment C: Following an overnight fast of at least 10 hours, 1 Gabapentin Extended-Release Tablet, 600 mg, Lot #: 06T4221, with 240 mL of ambient temperature water, 30 minutes after the start of a standardized meal (836 calories and less than 30% of calories from fat).

Gabapentin Extended-Release Tablets, 600 mg manufactured for Depomed, Inc., USA by (b) (4)

Treatment Periods:

Period I: June 7, 2006
Period II: June 14, 2006
Period III: June 21, 2006

Number of Subjects (planned and analyzed):

There were 24 subjects dosed in Period I, 22 of whom completed the study. One subject was dismissed because of an adverse event (AE), and 1 subject withdrew because of an AE. Pharmacokinetic and statistical analyses were performed on the 22 subjects who completed the study.

Blood Draw Timepoints:

During each study period, 16 blood samples were collected from each subject at the following timepoints: 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, and 48 hours post-dose.

Study 81-0048:

Name of Sponsor Company: Depomed, Inc. *Name of Finished Product:* Gabapentin Extended-Release Tablets, 600 mg *Name of Active Ingredient:* gabapentin	***For Sponsor Use Only***: Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***

Bioanalytical Procedure:

(b) (4)

[redacted]

Criteria for Evaluation:

The pharmacokinetic analysis was performed on 22 subjects who completed the 3 study periods. The safety assessment was performed on all subjects who received at least 1 dose during the course of the study.

Pharmacokinetics (PK):

The following pharmacokinetic parameters for gabapentin were calculated by standard non-compartmental methods: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and $t_{½}$.

Safety:

The incidences of all AEs were tabulated by treatment and subject number. Absolute values for vital signs, electrocardiogram (ECG) parameters, laboratory parameters and physical examinations were also documented and values outside the normal range were flagged. Shifts from baseline values were tabulated. AEs were documented using investigator and Medical Dictionary for Regulatory Activities (MedDRA) terms.

Statistical Methods:

Using General Linear Model (GLM) procedures in Statistical Analysis System (SAS), analysis of variance (ANOVA) was performed on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} and on untransformed $t_{½}$ at the significance level of 0.05. The intra-subject coefficient of variation (CV) was calculated using the Mean Square Error (MSE) from the ANOVA table. The ratio of geometric means and the 90% geometric confidence interval (90% C.I.) were calculated based on the difference in the Least Squares Means of the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} between the test and reference formulations. T_{max} was analyzed using nonparametric methods.

Study 81-0048:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended-Release Tablets, 600 mg	*Page:*	
Name of Active Ingredient: gabapentin		

Summary of Safety Results:

No serious adverse events (SAEs) were reported. One subject was dismissed because of an adverse event (AE), and 1 subject withdrew because of an AE.

There were a total of 25 AEs reported by 8 subjects during the study. Four subjects experienced a total of 4 AEs after administration of Gabapentin Extended-Release Tablets, 600 mg – fasting (Treatment A). Six subjects experienced a total of 9 AEs after administration of Gabapentin Extended-Release Tablets, 600 mg – fed (945 calories, > 50% from fat) (Treatment B). Two subjects experienced a total of 5 AEs after administration of Gabapentin Extended-Release Tablets, 600 mg – fed (836 calories, < 30% from fat) (Treatment C). Three subjects experienced a total of 7 end-of-study AEs. No AE occurred in 20% or more of the subjects, after administration of Gabapentin Extended-Release Tablets, 600 mg (Treatments A, B and C). Eleven AEs were "probably" related to the study drug. No significant safety concerns emerged.

Summary of Pharmacokinetic Results:

PHARMACOKINETIC PARAMETERS FOR GABAPENTIN:

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD		
	Gabapentin Extended-Release Tablets, 600 mg – fasting (A) (n=22)	Gabapentin Extended-Release Tablets, 600 mg – fed (945 calories, > 50% from fat) (B) (n=22)	Gabapentin Extended-Release Tablets, 600 mg – fed (836 calories, < 30% from fat) (C) (n=22)
AUC_{0-t} (ng·hr/mL)	19099 (57) 21966 ± 12432	49937 (29) 52066 ± 15301	29493 (40) 31399 ± 12439
AUC_{0-inf} (ng·hr/mL)	22282 (51) 24430 ± 12478†	51081 (29) 53173 ± 15377	30573 (38) 32435 ± 12468
C_{max} (ng/mL)	1941 (42) 2175 ± 923	3928 (20) 4002 ± 805	2812 (26) 2902 ± 749
T_{max} (hr)*	3.5 (1.0 - 10.0)	9.0 (4.0 - 12.0)	6.0 (3.0 - 10.0)
$t_{1/2}$ (hr)	8.7 ± 4.0†	5.7 ± 1.5	6.9 ± 1.9

* median (min – max)
† n = 19

Study 81-0048:

Name of Sponsor Company: Depomed, Inc. *Name of Finished Product:* Gabapentin Extended-Release Tablets, 600 mg *Name of Active Ingredient:* gabapentin	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***

Summary of Pharmacokinetic Results (Cont'd):

Relative Bioavailability Analysis of Gabapentin Extended-Release Tablets, 600 mg – fasting (A) versus Gabapentin Extended-Release Tablets, 600 mg – fed (945 calories, > 50% from fat) (B) for Gabapentin

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	32% to 46%	39%	35%
AUC_{0-inf}	39% to 52%	45%	27%
C_{max}	43% to 58%	50%	31%

Relative Bioavailability Analysis of Gabapentin Extended-Release Tablets, 600 mg – fasting (A) versus Gabapentin Extended-Release Tablets, 600 mg – fed (836 calories, < 30% from fat) (C) for Gabapentin

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	55% to 78%	65%	35%
AUC_{0-inf}	66% to 87%	76%	27%
C_{max}	59% to 81%	69%	31%

Relative Bioavailability Analysis of Gabapentin Extended-Release Tablets, 600 mg – fed (836 calories, < 30% from fat) (C) versus Gabapentin Extended-Release Tablets, 600 mg – fed (945 calories, > 50% from fat) (B) for Gabapentin

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	50% to 70%	59%	35%
AUC_{0-inf}	52% to 68%	60%	27%
C_{max}	61% to 84%	72%	31%

Study 81-0048:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only***: Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended-Release Tablets, 600 mg		
Name of Active Ingredient: gabapentin		

Conclusion:

The bioavailability of gabapentin is significantly increased in the presence of food. This is more pronounced with a high fat diet. This is most probably due to a longer residence time of the formulation in the upper GI tract, allowing for longer release duration of gabapentin where it is best absorbed. Study results suggest that Gabapentin ER tablets should be administered following a meal.

No SAEs were reported. Two subjects discontinued prematurely from the study because of AEs consisting of throbbing pain on right side of face and blood pressure increased. Overall, Gabapentin Extended-Release Tablets, 600 mg were well tolerated as a single-dose of 600 mg, administered under fasting and fed conditions, and no significant safety issues emerged.

Final Report Issue Date:
March 8, 2007

This study was performed in compliance with GCP.

Study 81-0049:

Name of Sponsor Company: Depomed, Inc. *Name of Finished Product:* Gabapentin Extended-Release Tablets, 600 mg *Name of Active Ingredient:* gabapentin	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***

Title of Study:

A Three-Way Crossover, Open-Label, Fed Study Comparing the Pharmacokinetic Profiles of Gabapentin Extended Release Tablets Versus Neurontin® Immediate Release Tablets on Day 1 and After 5 Days of Multiple Administration in Normal, Healthy, Non-Smoking Male and Female Subjects

Protocol No.: 3233 (81-0049)

Investigators:

Principal Investigator: Paul Y. Tam, M.D., F.R.C.P, F.A.C.P.

Sub-investigators: (b) (4)

Study Center:

Biovail Contract Research

- 460 Comstock Road, Toronto, ON, M1L 4S4 Canada
- 689 Warden Avenue, Unit 1, Toronto, ON, M1L 4R6 Canada

Publications based on this study:

None

Study Period:	*Phase of Development:*
June 20, 2006 to August 9, 2006	Phase I (bioavailability)

Objectives:

The primary objective of this study was to investigate the pharmacokinetics of gabapentin on Day 1 and on Day 8 (after 5 days of administration) of 2 different dosing regimens with Gabapentin Extended Release Tablets, 600 mg and three times daily (t.i.d.) dosing with Neurontin® (gabapentin) Tablets, 600 mg. The secondary objective of this study was to evaluate the safety of Gabapentin ER Tablets and Neurontin® IR Tablets on Day 1 and on Day 8 (after 5 days of administration) under fed conditions.

Main Criteria for Inclusion:

Normal, healthy, non-smoking male and female subjects between the ages of 18 and 65 years.

Study 81-0049:

Name of Sponsor Company: Depomed, Inc. *Name of Finished Product:* Gabapentin Extended-Release Tablets, 600 mg *Name of Active Ingredient:* gabapentin	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***

Test Product/Investigational Product, Lot Number and Mode of Administration:
Treatment A: 1 Gabapentin Extended Release Tablet, 600 mg in the morning (starting at 08:00) and 2 Gabapentin Extended Release Tablets, 600 mg in the evening (starting at 20:00), Lot #: 06T4221, administered orally with 240 mL of ambient temperature water.
Treatment B: 3 Gabapentin Extended Release Tablets, 600 mg in the evening (starting at 20:00), Lot #: 06T4221, administered orally with 240 mL of ambient temperature water.

Reference Product, Lot Number and Mode of Administration:
Treatment C: 1 Neurontin® (gabapentin) Tablet, 600 mg three times per day (starting at 08:00, 14:00, and 20:00), Lot #: 01716V, administered orally with 240 mL of ambient temperature water.

Treatment Periods:
Period I: June 21, 2006 and June 24, 2006 to June 28, 2006
Period II: July 11, 2006 and July 14, 2006 to July 18, 2006
Period III: July 31, 2006 and August 3, 2006 to August 7, 2006

Number of Subjects (planned and analyzed):
There were 24 subjects dosed in Period I, 21 of whom completed the study. One subject was dismissed because of an adverse event (AE), 1 subject was dismissed after emesis within 8 hours of dosing (for Treatment C), and 1 subject was dismissed because of administrative reasons. Pharmacokinetic and statistical analyses were performed on the 21 subjects who completed the study.

Blood Collection:
During the study, 128 blood samples (4 mL each) were collected from each subject. Approximately 542 mL and 557 mL of blood will be taken from male and female subjects, respectively.

Study 81-0049:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended-Release Tablets, 600 mg		
Name of Active Ingredient: gabapentin		

Bioanalytical Procedure:

(b) (4)

[redacted]

Criteria for Evaluation:

The pharmacokinetic analysis was performed on 21 subjects who completed the 3 study periods. The safety assessment was performed on all subjects who received at least 1 dose during the course of the study.

Pharmacokinetics (PK):

The following pharmacokinetic parameters for gabapentin were calculated by standard non-compartmental methods:

Day 1: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, T_{maxrel} and $t_{1/2}$.

Day 8: AUC_{τ}, AUC_{0-24}, C_{max}, C_{trough}, C_{min}, C_{ave}, T_{max}, T_{maxrel} % Fluctuation, and % Swing.

Safety:

The incidences of all adverse events (AEs) were tabulated by treatment and subject number. Absolute values for vital signs, electrocardiogram (ECG) parameters, laboratory parameters and physical examinations were also documented and values outside the normal range were flagged. Shifts from baseline values were tabulated. AEs were documented using investigator and Medical Dictionary for Regulatory Activities (MedDRA) terms.

Study 81-0049:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended-Release Tablets, 600 mg	*Page:*	
Name of Active Ingredient: gabapentin		

Statistical Methods:
Results of a descriptive analysis for the PK parameters are presented. Exploratory analysis on PK parameters was conducted to look at differences between treatments using ANOVA and nonparametric methods. In addition, the ratio (Test/Reference) of geometric least square means (LSMs) and its 90% confidence intervals (CI) were calculated. The parameter T_{max} was evaluated using nonparametric methods.

Summary of Safety Results:
No serious adverse events were reported. One subject was dismissed due to an AE.

There were a total of 58 AEs reported by 17 subjects in the study. No AE occurred in 20% or more of the subjects, after administration of Gabapentin Extended-Release Tablets, 600 mg or Neurontin® (gabapentin) Tablets, 600 mg. Eighteen AEs were "possibly" related to the study drug. All subjects who experienced AEs during this study recovered completely, with the exception of 1 subject who was lost to follow-up. No significant safety concerns emerged.

Summary of Pharmacokinetic Results:
Summary statistics of pharmacokinetic parameters of gabapentin on Day 1 in healthy subjects (Treatments A, B & C)

Pharmacokinetic Parameters	**Geometric Mean (%CV) Arithmetic Mean ± SD**		
	Gabapentin Extended-Release Tablets, 600 mg (1 in the morning/ 2 in the evening) (A) (n=21)	**Gabapentin Extended-Release Tablets, 600 mg (3 in the evening) (B) (n=21)**	**Neurontin® (gabapentin) Tablets, 600 mg (3 times per day) (C) (n=21)**
AUC_{0-t} (ng·hr/mL)	136528 (20) 138858 ± 27238	116545 (26) 120235 ± 31304	129161 (23) 132482 ± 31010
AUC_{0-inf} (ng·hr/mL)	142063 (20) 144491 ± 28619	120322 (26) 124008 ± 32144[a]	135545 (23) 139010 ± 32206[b]
C_{max} (ng/mL)	6847 (21) 6997 ± 1480	7706 (27) 7974 ± 2157	7311 (20) 7455 ± 1496
T_{max} (hr)*	20.0 (16.0 - 24.0)	8.0 (4.0 - 12.0)	14.0 (4.0 - 16.0)
T_{maxrel} (hr)*	8.0 (4.0 - 12.0)	8.0 (4.0 - 12.0)	2.0 (1.0 - 4.0)
$t_{1/2}$ (hr)	7.4 ± 1.5	9.1 ± 3.2[a]	8.4 ± 1.9[b]

* median (min – max)
[a] n = 20
[b] n = 19

Study 81-0049:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended-Release Tablets, 600 mg	*Page:*	
Name of Active Ingredient: gabapentin		

Summary of Pharmacokinetic Results (Cont'd):

Comparison of pharmacokinetic parameters of gabapentin on Day 1 in healthy subjects (Treatments A, B & C)

Treatment A versus Treatment B

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	108% to 128%	118%	16%
AUC_{0-inf}	110% to 129%	119%	15%
C_{max}	81% to 98%	89%	19%

Treatment A versus Treatment C

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	97% to 116%	106%	16%
AUC_{0-inf}	97% to 114%	105%	15%
C_{max}	85% to 103%	94%	19%

Treatment B versus Treatment C

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-t}	83% to 98%	90%	16%
AUC_{0-inf}	81% to 96%	88%	15%
C_{max}	95% to 116%	105%	19%

Study 81-0049:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended-Release Tablets, 600 mg	*Page:*	
Name of Active Ingredient: gabapentin		

Summary of Pharmacokinetic Results (Cont'd):

Summary statistics of pharmacokinetic parameters of gabapentin at steady state in healthy subjects (Treatments A, B & C)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD		
	Gabapentin Extended-Release Tablets, 600 mg (1 in the morning/ 2 in the evening) (A) (n=21)	Gabapentin Extended-Release Tablets, 600 mg (3 in the evening) (B) (n=21)	Neurontin® (gabapentin) Tablets, 600 mg (3 times per day) (C) (n=21)
AUC_{0-24} (ng·hr/mL)	141431 (22) 144605 ± 31171	128790 (26) 132808 ± 34701	138455 (21) 141301 ± 29759
C_{trough} (ng/mL)	6097 ± 1609	2043 ± 702	3701 ± 1201
C_{max} (ng/mL)	7846 (23) 8048 ± 1819	9326 (24) 9585 ± 2326	8377 (20) 8536 ± 1715
C_{min} (ng/mL)	3775 (33) 3964 ± 1311	1747 (35) 1842 ± 654	2476 (30) 2588 ± 783
C_{ave} (ng/mL)	6025 ± 1300	5534 ± 1446	5885 ± 1242
T_{max} (hr)*	18.0 (8.0 - 24.1)	8.0 (3.0 - 12.0)	8.0 (2.0 - 17.0)
T_{maxrel} (hr)*	6.0 (4.0 – 12.1)	8.0 (3.0 - 12.0)	2.0 (1.0 - 5.0)
Degree of Fluctuation (%)	69 ± 19	141 ± 20	102 ± 14
Degree of Swing (%)	113 ± 50	456 ± 177	246 ± 79

* median (min – max)

Comparison of pharmacokinetic parameters of gabapentin at steady state in healthy subjects (Treatments A, B & C)

Treatment A versus Treatment B

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-24}	102% to 117%	110%	13%
C_{max}	78% to 91%	84%	15%
C_{min}	193% to 237%	214%	20%

Treatment A versus Treatment C

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-24}	95% to 109%	102%	13%
C_{max}	87% to101%	94%	15%
C_{min}	138% to 169%	153%	20%

Study 81-0049:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended-Release Tablets, 600 mg	*Page:*	
Name of Active Ingredient: gabapentin		

Summary of Pharmacokinetic Results (Cont'd):
Treatment B versus Treatment C

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-24}	87% to 100%	93%	13%
C_{max}	103% to 121%	112%	15%
C_{min}	64% to 79%	71%	20%

Conclusion:
The objective of the study was to assess the pharmacokinetics of Gabapentin ER formulations with different dosing regimens on Day 1 and at steady state on Day 8. As a secondary (exploratory) objective, the test formulations were compared to the reference product Neurontin® immediate release formulation.

In both the treatments, A and B, Gabapentin ER formulations reached steady state by Day 8.

Both test treatment regimens A and B demonstrated similar systemic exposure of gabapentin to that obtained from Neurontin® after both single dose administration and at the steady state. Treatment A had a similar C_{max} while regimen B resulted in a C_{max} approximately 12% higher compared to that of Neurontin® given tid at steady state. After the single dose administration, Treatment A peak absorption of gabapentin was about 6% lower compared to that from Neurontin® tid, while Treatment B was about 5% greater. At steady state, treatment A achieved a higher C_{min} than that of both regimen B and Neurontin®.

Overall, Treatment regimen A (1 Gabapentin Extended Release Tablet, 600 mg in the morning and 2 Gabapentin Extended Release Tablets, 600 mg in the evening) and Treatment regimen B (3 Gabapentin Extended Release Tablets, 600 mg in the evening) demonstrated comparable overall absorption of gabapentin to the reference formulation of Neurontin® immediate release formulation.

Study 81-0049:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only:*** Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Product: Gabapentin Extended-Release Tablets, 600 mg		
Name of Active Ingredient: gabapentin		

Conclusion (Cont'd):

No SAEs were reported. One subject discontinued prematurely from the study because of an AE consisting of 1 degree AV block. All subjects who experienced AEs during this study recovered completely, with the exception of 1 subject who was lost to follow-up.

Overall, Gabapentin Extended-Release Tablets, 600 mg were well tolerated when administered in the fed state as a single dose or as a multiple-dose of 1800 mg per day and no significant safety issues emerged.

Revised Final Report Issue Date:
January 13, 2010

This study was performed in compliance with GCP.

Study 81-0050:

Name of Sponsor Company: Depomed, Inc.	***For Sponsor Use Only***: Individual Study Table Referring to Part of the Dossier *Volume:* *Page:*	***For National Authority Use Only:***
Name of Finished Products: Gabapentin ER Tablets, 600 mg (fast and standard releasing) Gabapentin ER tablets, 300 mg (slow releasing)		
Name of Active Ingredient: gabapentin		

Title of Study:

A Four-Way Crossover, Open-Label, Single-Dose, Fed, Pharmacokinetic Study Of 3 Formulations Of Gabapentin Extended Release (ER) Tablets And Neurontin® Immediate Release (IR) 600 mg Tablets In Healthy, Non-Smoking Male And Female Subjects For Investigation Of *In-Vitro/In-Vivo* Correlation

Protocol No.: 3234 (81-0050)

(b) (4)

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4 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

4.3 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology **New Drug Application Filing and Review Form**			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	***NDA*-022544**	**Brand Name**	***GRALISE***
OCP Division (I, II, III, IV, V)	***II***	**Generic Name**	***Gabapentin***
Medical Division		**Drug Class**	***Propionic acid derivative***
OCP Reviewer	***Suresh B Naraharisetti***	**Indication(s)**	Management of postherpetic neuralgia
OCP Team Leader	***Suresh Doddapaneni***	**Dosage Form**	***Extended- release tablet***
Pharmacometrics Reviewer		**Dosing Regimen**	
Date of Submission	**03/30/2010**	**Route of Administration**	***Oral***
Estimated Due Date of OCP Review		**Sponsor**	**Abbott**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**		
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**3**		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping		**1**		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan		**1**		**Sponsor is requesting a waiver**
Literature References				
Total Number of Studies		**9**	**9**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR	X			

	requirements?				
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Suresh Babu Naraharisetti	November 08, 2010
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni	November 08, 2010
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURESH B NARAHARISETTI
12/06/2010

VENKATESH A BHATTARAM
12/06/2010

YANING WANG
12/06/2010

SURESH DODDAPANENI
12/06/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 22-544 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DAAP		
Sponsor:	Abbott	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	--	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Gabapentin ER tablets	**Date Assigned:**	September 22, 2010
Indication:	Management of postherpetic neuralgia	**Date of Review:**	November 22, 2010
Formulation/strengths	Extended Release tablets/ 300 mg and 600 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
March 30, 2010	March 30, 2010	Sep 22, 2010	1/10/11
Type of Submission:	Original NDA		
Type of Consult:	- IVIVC model - Dissolution method and specifications - (b) (4) - In vitro alcohol interaction study		

REVIEW SUMMARY:

Neurontin® (gabapentin hydrochloride) immediate release tablets were approved by the Agency on May 2002 under NDA 21-424 for the management of PHN in adults.

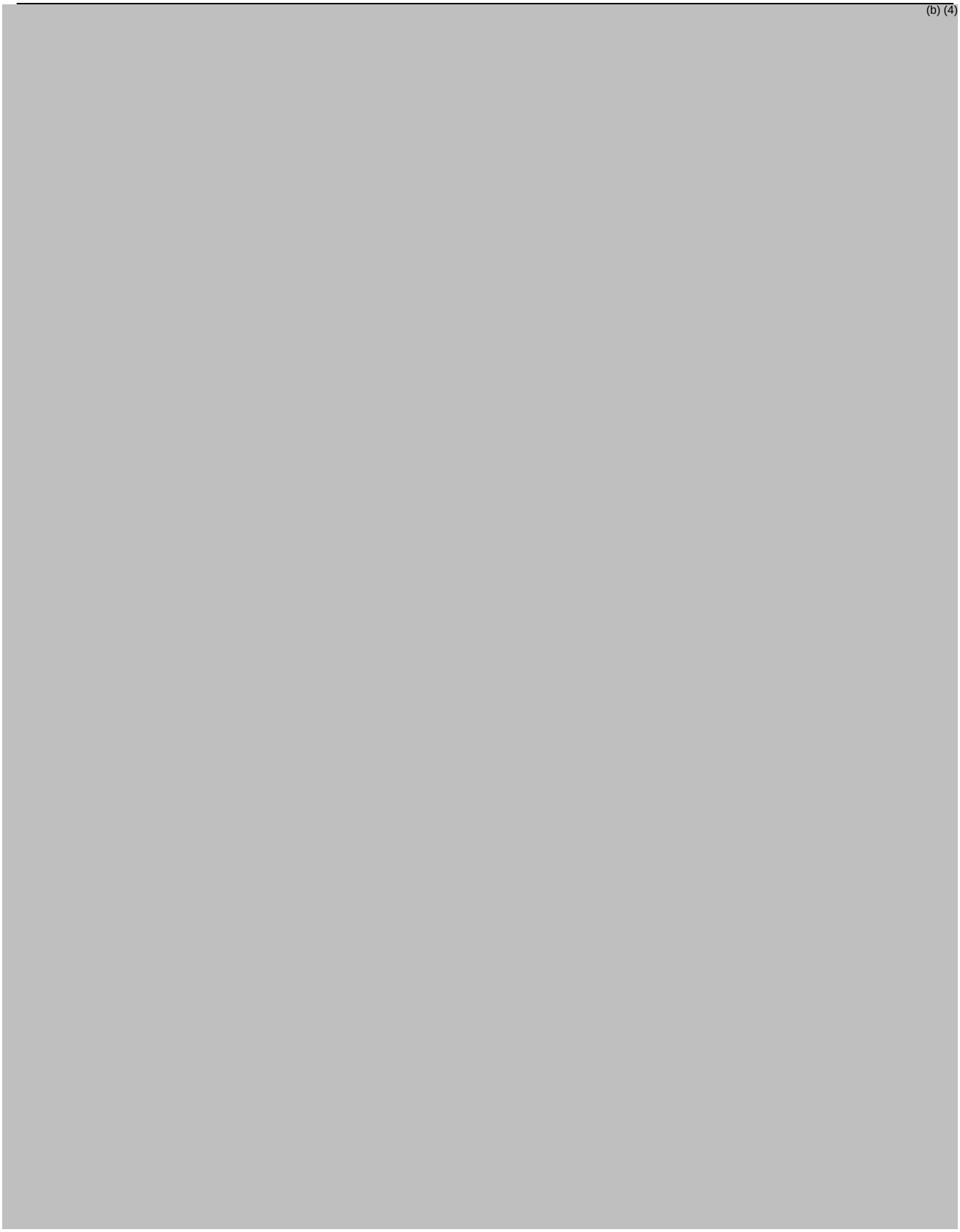
The sponsor developed a new formulation for gabapentin hydrochloride (HCl) consisting of an extended release tablet for the once daily management of PHN in adults. The gabapentin HCl ER tablets will be marketed in the United States as 300 mg and 600 mg strengths. The two strengths are not proportionally similar in composition.

The clinical development program for this new drug formulation consisted of single and multiple dose PK studies, a food effect study, phase 2 and phase 2 supportive studies, and a pivotal Phase 3 confirmatory trial which evaluated the safety and efficacy of the highest proposed dose. (b) (4) . This review focuses on the Biopharmaceutics evaluation and acceptability of **1)** the IVIVC model, **2)** the dissolution method and specifications, **3)** (b) (4) , and **4)** an in vitro alcohol dose dumping study.

1. In Vivo-In Vitro Correlation

(b) (4)

(b) (4)



(b) (4)

2. Proposed Dissolution Method and Specifications:

The dissolution method and specifications being proposed by the sponsor for Gabapentin® ER Tablets are as follow:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Gabapentin HCl	ER Tablet	I (Basket)	100	pH 1.2 Buffer, modified Simulated Gastric Fluid without pepsin	900, 37 °C ± 0.5 °C	1 hour: (b) (4) 4 hours: (b) (4) 8 hours: (b) (4) 12 hours: (b) (4)

The proposed dissolution method is acceptable. According to the sponsor, the above proposed acceptance criteria are based on the mean in-vitro dissolution profile for gabapentin HCl ER tablets used in the clinical/registration/stability data for and the IVIVC model. As stated above, the IVIVC models were found unacceptable; therefore, the above proposed dissolution specification are also not acceptable since at the 8 hr time point the percent of variation is higher than (b) (4). This reviewer recommends different dissolution specifications which are based on the mean in-vitro dissolution profiles for gabapentin HCl extended-release tablets calculated from the available lot release/clinical data (6 batches). The recommended dissolution specifications are also met by the stability batches studies up to 36 months at different conditions.

3. (b) (4)

(b) (4) The approval of this formulation should be based on the results of an acceptable BE study or an approved IVIVC.

4. In Vitro Alcohol Dose Dumping:

No dose-dumping from the gabapentin ER tablets was observed when dissolved in up to 40% ethanol. On the contrary, the release profiles became slower in the presence of alcohol.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 22-544 (000) submitted on March 30, 2010 and October 29, 2010 for Gabapentin ER tablets. We found the proposed IVIVC models NOT acceptable. The sponsor's proposed dissolution specifications need to be revised. The following comments should be conveyed to the sponsor:

1. The sponsor's proposed IVIVC models for Gabapentin ER tablets are not acceptable for the following reasons:
   a. (b) (4)
   .
   b. (b) (4)

c. (b) (4)
.

d. (b) (4)

2. (b) (4)
. Since the sponsor failed to demonstrate the extended release characteristics as outline in 21 CFR 320.25(f), this proposed formulation of gabapentin should not be classified as an extended release product.

3. (b) (4)

4. Using the dissolution method; USP Apparatus 1 (basket), 100 rpm, 900 ml of pH 1.2 Buffer, modified Simulated Gastric Fluid without pepsin, at 37°C, the following dissolution acceptance criteria are recommended for gabapentin ER tablets:

Acceptance Criteria	
1 hour:	(b) (4)
4 hours:	(b) (4)
8 hours:	(b) (4)
12 hours:	(b) (4)

In the absence of an acceptable IVIVC, the recommended specification ranges are based on the mean dissolution values (b) (4) from the registration, clinical and stability batches. Please revise the dissolution specifications accordingly.

Comment for the Review Team

1. As noted above, the plasma concentrations of gabapentin ER tablets have a higher fluctuation index as compared to that for Neurontin IR tablets. In addition, the systemic exposure is highly dependant of the type of meal (e.g. fat content). Therefore, the MO should evaluate the impact of the wide fluctuation and high variability observed for the drug's plasma concentrations for this gabapentin formulation on the efficacy and safety of the product. An effort to minimize this variability should be attempted either by reformulation or by detailed dosing administration instructions.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

c.c: ADorantes, YHu, Dchristodoulou, RRoca, Efields, Rshibuya, Awasserman, SNasaharisetti, ABhattaram

INTRODUCTION

Neurontin® (gabapentin hydrochloride) immediate release tablets were approved by the Agency in May 2002 under NDA 21-424 for the management of PHN in adults. The approved dose for Neurontin in adults with PHN is 1800 mg/day, administered in 3 divided doses.

The sponsor has developed a new formulation for gabapentin hydrochloride being submitted under 505(b)(2) of the FD&C Act, therefore, the Sponsor is relying on the Divisions findings of preclinical toxicology and safety conducted on Neurontin® to support this application. This new formulation of Gabapentin is an extended Release tablets formulation (G-ER) consisting of two strengths, 300 mg and 600 mg, that are intended for once-daily (QD) administration of 1800 mg for the management of Post Herpetic Neuralgia (PHN) in adults. The sponsor states that G-ER tablets given QD is designed to provide comparable exposure, measured by the area under the plasma concentration-time curve (AUC), to the immediate release (IR) product (Neurontin®) given three-times daily (TID). G-ER tablets are expected to provide an improved safety profile compared to the currently available Neurontin® tablets and capsules.

The two strengths are proportionally similar in composition. The clinical development program for this new drug formulation consisted of six single and multiple dose PK study including a food effect study, phase 2 and phase 3 supportive studies, and a pivotal Phase 3 confirmatory trial which evaluated the safety and efficacy of the highest proposed dose. One clinical pharmacology study was utilized for the construction of a Level A in vivo in vitro correlation (IVIVC). This review focuses on the acceptability of the IVIVC model, dissolution method and specifications, (b) (4), and an in vitro alcohol interaction study.

CHEMISTRY

Drug Substance

Gabapentin is amphoteric and has two pKa's, 3.7 and 10.7 due to the carboxylic acid group and the primary amine group, respectively. Gabapentin predominantly exists as a cation at acidic pH, an anion at basic pH and as a zwitterion at intermediate values of pH between the two pKa values. The neutral species does not exist to any appreciable extent due to the large separation of the two pKa values.

Gabapentin is freely soluble in water, 0.1 N HCl, 0.1 N NaOH and glacial acetic acid. Theoretically, the solubility of gabapentin as a function of pH is determined by the proportion of the various species of gabapentin present in solution. Small difference at different pH values implies that the solubilities of the cationic and zwitterionic forms are not very different, and that there is only a weak dependence. The solubilities of gabapentin drug substance in deionized water, modified simulated gastric fluid (mSGF, pH 1.2), modified simulated intestinal fluid (mSIF, pH 6.8) and acetate buffer (pH 4.5) at 37 °C are 135 mg/ml, 166 mg/ml, 139 mg/ml, and 153 mg/ml, respectively. Gabapentin HCl is being classified in the literature as BCS class III drug.

Formulation

G-ER 300 mg tablets are white to off-white, film-coated, 0.3937" X 0.6299" modified oval shaped tablets that are 714.0 mg in weight, and debossed with "SLV" on one side and with "300" on the other side. The tablet contains 300 mg of gabapentin active. The composition of the 300 mg tablet is summarized in Table 1.

G-ER 600 mg tablets are beige, film-coated, 0.4330" x 0.7450" modified oval shaped tablets that are 1020.0 mg in weight, and debossed with "SLV" on one side and with "600" on the other side. The tablet contains 600 mg of gabapentin active. The composition of the 600 mg tablet is summarized in Table 2.

Table 1. Components and composition for Gabapentin ER Tablets, 300 mg

Component[3]	Quantity [mg/tablet]	w/w [%]
	(b) (4)	
Gabapentin	300.00	(b) (4)
Polyethylene Oxide	(b) (4	
Hydroxypropyl Methylcellulose (Hypromellose)		
Microcrystalline Cellulose		
Copovidone		
(b) (4)		
Magnesium Stearate		
(b) (4)		
	(b) (4)	
(b) (4)	(b) (4)	
Opadry® II White		
(b) (4)		
Total Coated Tablet	**714.00**	
	(b) (4)	
(b) (4)		

3 All excipients with the exception of Opadry® II White are tested according to the corresponding monographs in the current editions of the NF/USP/EP.

Table 2. Quantitative Composition of G-ER Tablets, 600 mg

Component[3]	Quantity [mg/tablet]	w/w [%]
	(b) (4)	
Gabapentin	600.00	(b) (4)
Polyethylene Oxide	(b) (4)	
Hydroxypropyl Methylcellulose (Hypromellose)		
Copovidone		
(b) (4)		
Magnesium Stearate		
(b) (4)		
	(b) (4)	
(b) (4)	(b) (4)	
Opadry® II Beige		
(b) (4)		
Total Coated Tablet	**1020.00**	
(b) (4)		
(b) (4)		

3 All excipients with the exception of Opadry® II White are tested according to the corresponding monographs in the current editions of the NF/USP/EP.

Formulation Overview

The Sponsor commenced the G-ER development program with (b) (4) formulations, and initiated a dog toxicity study (Study Report: 80-0014), and three PK studies 81-0008, 81- 0040, and 81-0044 with this formulation. The formulations were optimized after these studies to limit the growth of (b) (4) formation, the major degradant of gabapentin, by changing to a (b) (4) formulation, and PK studies 81-0048, 81-0049, and 81-0050 were conducted using this formulation. The Phase 3 clinical study (81-0062) in this indication was conducted using the To-Be-Marketed formulation, i.e., the (b) (4) formulation, and the Phase 2 study (81-0038) was conducted with the (b) (4) formulation. The components and composition of the formulation used in Phase 2 studies is shown in Figure 2a.

Table 2a. Quantitative Composition of G-ER Tablet in the Phase 2 Formulations

Reviewer's Comments
Refer to section below on data supporting the linkage between Phase 2 and Phase 3 data.

Phase 3/Registration batches of 300 mg and 600 mg G-ER tablets were coated with Opadry® II White (b) (4), and debossed with "DEPOMED" on one side and either "300" or "600", relative to the dosage, on the other side. In order to differentiate between the dosage strengths, new film coats and deboss will be incorporated into the To-Be-Marketed final product. The 300 mg dosage strength will remain coated with an Opadry® II White and debossed with "SLV" on one side and "300" on the other side. The 600 mg dosage strength will be coated with Opadry® II Beige (b) (4) and debossed with "SLV" on one side and "600" on the other side.

Reviewer's Comments
Based on an email communication, Dr. Young Hu considers the changes done to the to-be-marketed formulation as Level 2 according to the SUPAC MR guidance. The sponsor submitted dissolution profiles comparison to support this change (see section below on data supporting the linkage between phase 3 and the to-be marketed formulation).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA SUAREZ
12/03/2010

PATRICK J MARROUM
12/03/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 870)** **Tracking/Action Sheet for Formal/Informal Consults**

From: Suresh Babu Naraharisetti, Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 05/05/2010	IND No.: Serial No.:	NDA No. 022544	DATE OF DOCUMENT 03/30/2010	
NAME OF DRUG **Gabapentin (GRALISE)**	PRIORITY CONSIDERATION		Date of informal/Formal Consult: 03/30/2010	
NAME OF THE SPONSOR: **[Abbott]**				

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW):* *Filing Meeting*
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☒ See comments below
☐Medical ☐Chemist ☐Pharm-Tox	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See submission cover letter
☐Micro ☐Pharmacometrics ☐Others		☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)		

REVIEW COMMENT(S)

☒ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

BACKGROUND/COMMENTS TO SPONSOR:

Abbott submitted NDA, gabapentin extended release tablets (G-ER), of strengths 300 and 600 mg for management of postherpetic neuralgia. This application was submitted under section 505 (b) (2) of the Federal Food Drug and Cosmetic Act and the referenced drug is gabapentin IR formulation, (Neurontin® NDAs 20-129, 20-235, 20-882, 21-397, 21-423, 21-424). The proposed QD dose- titration schedule with evening meal is:

	Day 1	Day 2	Day 3-6	Day 7-10	Day 11-14	Day 15
Daily dose	300 mg	600 mg	900 mg	1200 mg	1500 mg	1800 mg

The proposed G-ER formulation is a gastro-retentive formulation. When administered with a meal, the G-ER tablet swells to a size that promotes gastric retention for several hours in the fed state. During this time drug is gradually released over ~ 8- 10 hr period to the upper GI tract where the gabapentin is best absorbed. Similar gastro- retentive formulations approved by the agency includes Glumetza (metformin HCI ER Tabs) and Proquin XR (ciprofloxacin HCl).

For this G-ER formulation, the sponsor claims that QD administration with the evening meal results in peak concentrations in the middle of the night results low incidence of somnolence and dizziness, while improving the quality and duration of sleep compared with multiple daytime peaks with TID administration of IR product.

In support of this NDA, sponsor conducted:

- 6 PK studies in healthy volunteers in the fed state
  1) Pilot **Study 81-0008**: In this study **Relative BA** of 3 pilot ER formulations were compared with IR Neurontin

2) **Study 81-0040**: **Dosage-Form Proportionality/Relative BA**: This was a four way crossover study that assessed a) dosage form proportionality of two lots (# 1079 and 1082) of 300 mg G-ER formulations administered as 300 mg x 2 versus G-ER 600 mg x1 (Lot # 1082) and b) relative BA of G-ER 600 mg versus Neurontin IR 600 mg. The study was conducted in fed state with drugs treatments administered 20 minutes after the start of a standardized, ~ 500-600 calorie, moderate-fat (approximately 40%) content meal .

3) **Study 81-0044**: **Dose Proportionality**: Dose- Proportionality study of four dose levels of G-ER administered as multiples of 600 mg viz., 600 x 1 (600 mg), 600 x 2 (1200 mg), 600 x 3 (1800 mg) and 600 x 4 (2400). The study was conducted in fed state with drugs treatments administered 20 minutes after the start of a standardized, ~ 500-600 calorie, moderate-fat (approximately 40%) content meal .

4) **Study 81-0048**: **Food Effect**: This was a three-way cross over study that assessed the relative BA of G-ER tablets administered under fasted versus two fed conditions (with different fat percentages from meal). Each subject received one 600 mg G-ER tablet after a low-fat meal (836 kcal, < 30% fat), after a high-fat meal (945 kcal, > 50% fat), or or after an overnight fast in a randomized order

5) **Study 81-0049**: **Multiple Dosing**: This three way cross over study compared the relative BA of G-ER tablets versus Neurontin IR tablets administered on Day 1 and after 5 days of multiple administration. Subjects received in randomized order, 1800 mg G-ER tablets QD (evening dose), 1800 mg G-ER tablets BID (600 mg in the morning, 1200 mg in the evening), or 1800 mg Neurontin tablets (600 mg TID). All doses were administered 30 minutes after a high-fat content meal (50% calories from fat).

6) Pharmacokinetic Modeling and Simulation for **Dosing in Renally Impaired Subjects** (85-0009 and 85-0010): Gabapentin plasma concentration data from 3 pharmacokinetic studies (81-0040, 81-0044 and 81-0048) was used to construct a compartmental PK model and to stimulate the dosing for patients with renal impairment.

- In addition ,
  7) Study 81-0050: IVIVC Correlation Study

- 3 Clinical efficacy studies comprising of one Phase 2 Study, 81-0038 (both 1800 mg QD and asymmetric BID dosing) and two Phase 3 studies, 81-0062 (QD) and 81-0045 (both 1800 mg QD and asymmetric BID dosing).

The conducted PK studies meet the regulatory requirements for filing and this application is filable from the clinical pharmacology perspective. However with regard to the discrepancy in renal dosing schedule from the conclusion of the simulation study (85-0010) and the annotated label, the following comments is it to be communicated to the sponsor in 74-day letter.

- *"Clarify the discrepancy in the proposed renal dosing schedule for the 'moderate renally impaired group' in the annotated package insert (600 mg to 1800 mg QD) and the final conclusion of 600 mg or 1200 mg QD in the simulation report (Study Report: 85 0010).*
- *Unlike in Neurontin products, you have not proposed the dosing scheme for patients with creatinine clearance ≤ 15 ml/min and for patients undergoing hemodailysis. Propose the dosing scheme for patients with creatinine clearance ≤ 15 ml/min and patients undergoing hemodailysis or provide an explanation if dosing in these patients is not practically feasible with your product.*

The Clinical Pharmacology filing check list and fling meeting slides are attached as attachment-1 and attachment-2, respectively to this tracking sheet.

SIGNATURE OF REVIEWER: Suresh Babu Naraharisetti, Ph.D. **SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.**	Date 05/11/2009 Date 05/11/2009
CC.: HFD # [ ]; TL: [ ]	**Project Manager:** **Date**

5 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	***NDA***-022544	**Brand Name**	***GRALISE***
OCP Division (I, II, III, IV, V)	***II***	**Generic Name**	***Gabapentin***
Medical Division		**Drug Class**	***Propionic acid derivative***
OCP Reviewer	***Suresh B Naraharisetti*** ***David Lee***	**Indication(s)**	Management of postherpetic neuralgia
OCP Team Leader	***Suresh Doddapaneni***	**Dosage Form**	***Extended- release tablet***
Pharmacometrics Reviewer		**Dosing Regimen**	
Date of Submission	**03/30/2010**	**Route of Administration**	***Oral***
Estimated Due Date of OCP Review		**Sponsor**	**Abbott**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non fasting single dose:	**X**	**1**		
fasting / non fasting multiple dose:				
Drug-drug interaction studies -				
In vivo effects on primary drug:				
In vivo effects of primary drug:				
In vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

geriatrics:				
renal impairment:	**X**	**1**		
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**3**		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping		**1**		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan		**1**		**Sponsor is requesting a waiver**
Literature References				
Total Number of Studies		**9**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)						
	Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Suresh Babu Naraharisetti	May 12, 2010
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni	May 12, 2010
Team Leader/Supervisor	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22544	ORIG-1	ABBOTT PRODUCTS INC	GABAPENTIN E-R TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURESH B NARAHARISETTI
05/26/2010

SURESH DODDAPANENI
05/26/2010
I Concur