CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022544Orig1s000

SUMMARY REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

Summary Review for Regulatory Action

Date	January 28, 2011
From	Bob A. Rappaport, M.D. Director Division of Anesthesia and Analgesia Products
Subject	Division Director Summary Review
NDA #	022544
Applicant Name	Abbott Products, Inc.
Date of Submission	March 30, 2010
PDUFA Goal Date	January 30, 2011
Proprietary Name / **Established (USAN) Name**	Gralise Gabapentin
Dosage Forms / Strength	300 mg and 600 mg Tablets
Proposed Indication	For the management of postherpetic neuralgia
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Timothy Jiang, M.D., Ph.D.
Statistical Review	Yongman Kim, Ph.D.; Dionne Price, Ph.D.;
Pharmacology Toxicology Review	Armaghan Emami, Ph.D.; Adam Wasserman, Ph.D.
CMC/Quality Review	Yong Hu, Ph.D.; Prasad Peri, Ph.D.
CMC/Biopharmaceutics	Sandra Suarez Sharp, Ph.D., Angelina Dorantes, Ph.D., Patrick Marroum, Ph.D.
Clinical Pharmacology Review	Atul Bhattaram, Ph.D.; Yaning Wang, Ph.D.; Suresh Naraharisetti, Ph.D.; Suresh Doddapaneni, Ph.D.
DDMAC	Kathleen Klemm, Pharm,D., Twayla Thompson, Pharm.D., Mathilda Fienkeng, Pharm.D.
DSI	Susan Liebenhaut, M.D., Tejashri Purohit-Sheth, M.D.
CDTL Review	Ellen Fields, M.D., M.P.H.
OSE/DPV II	Martin Pollock, Pharm.D.; Lauren Choi, Pharm.D.; Mark Avigan, M.D.;
OSE/DMEPA	Carlos M. Mena-Grillasca, RPh., Judy Park, Pharm.D.; Denise Toyer, Pharm.D., Carol Holquist, R.Ph.
OSE/DRISK	Shawna L Hutchins, M.P.H., R.N.; Claudia Karwoski, Pharm.D.

OND Office of New Drugs
DDMAC Division of Drug Marketing, Advertising and Communication
OSE Office of Surveillance and Epidemiology
DMEPA Division of Medication Error Prevention
DSI Division of Scientific Investigations
DRISK Division of Risk Management
CDTL Cross Discipline Team Leader
DPV II Division of Pharmacovigilance II

1. Introduction

Abbott Products, Inc. submitted NDA 022544 for Gralise (gabapentin tablets) for the management of postherpetic neuralgia (PHN) as a 505(b)(2) application referencing NDAs 021129 (epilepsy), 020235 (epilepsy), 020882 (epilepsy), 021397 (PHN), 021423 (PHN) and 021424 (PHN), all of which are for Neurontin, gabapentin immediate-release tablets. The PHN application was approved in May of 2002.

Gabapentin is thought to provide analgesia in neuropathic pain at least in part by binding to α2δ calcium channel subunits of voltage-gated N-type Ca^{2+} ion channels and thereby preventing entry of Ca^{2+} into neurons, leading to reduced neurotransmitter release and attenuation of postsynaptic excitability. This new formulation was designed as a gastric-

retentive tablet intended for once daily dosing. When administered with food, the tablet swells to a size that the applicant claims results in gastric retention for several hours, allowing for more prolonged release of the active component in the upper gastrointestinal tract where gabapentin is more effectively absorbed. Products with similar gastric-retentive technology have been found to be safe and effective and have been approved by the Agency.

2. Background

As this application is relying on the Agency's previous finding of safety and efficacy for Neurontin, which carries an indication for PHN, during development the division agreed that only a single adequate and well-controlled study would be required to establish the efficacy of the new formulation. While the clinical review team found the application to be approvable, as did the CMC, pharmacology/toxicology and clinical pharmacology teams, the biopharmaceutics review team found deficiencies in this application that included: 1) the IVIVC model is unacceptable, (b) (4) along with the fact that the extended-release properties of the product are controlled by the presence or absence of food rather than by the formulation itself, would not allow for the applicant to claim that Gralise is an extended-release product. Further details about these concerns and the clinical team's opinions regarding them are included in Section 5 of my review.

3. CMC

The following summary of key CMC information has been reproduced from pages 3 and 4 of Dr. Fields' review:

> The extended drug release is claimed to be achieved by the diffusional control of the drug in the matrix of the polymers (b) (4), which also control the swelling of the tablets. The tablet swelling has been shown by the significant weight gain in simulated gastric fluid from an in vitro study, however no data has been provided regarding the swelled tablet size, nor is there in vivo data. The tablet is said to exit the stomach during Phase III of the migrating motor complex in the fasting state and to transit through the GI tract and dissolve away.
>
> The 300mg tablets are white to off-white, film-coated, modified oval shaped tablets, and debossed with "SLV" on one side and 300 on the other side. The 600mg tablets are beige, film-coated, modified oval shaped tablets, and debossed with "SLV" on one side and 600 on the other side.
>
> The excipients for both strength tablets are polyethylene oxide, hypromellose, copovidone, magnesium stearate (b) (4), microcrystalline cellulose (300mg), Opadry II white (300mg) and beige (600mg). The commercial manufacturing site for the drug product is (b) (4)
>
> … The applicant provided long-term stability data for three registration batches of each strength in both bottle and blister packaging configurations. The registration batches were

shown to be stable over 24 - 36 months at the long-term storage condition (25 ºC / 60%RH). The applicant also provided the stability data for one batch of 600mg tablets with the commercial dress (deboss and color). The stability of the commercial 600 mg tablets was comparable to the phase 3/registration batches over 3 months at long-term condition (25 ºC / 60%RH) and the accelerated condition (40 ºC / 75%RH).

An in-vitro study showed that the drug release is decreased with increasing concentration of alcohol in the dissolution medium, suggesting a low risk of dose dumping in the presence of alcohol.

The manufacturing facilities have been deemed acceptable by the Office of Compliance.

4. Nonclinical Pharmacology/Toxicology

The following summary of the pharmacology/toxicology review team's conclusions has been reproduced from page 6 of Dr. Fields' review:

> In summary, the route of administration, daily dosage, duration of use of G-ER and human AUC and Cmax values at the maximum recommended human dose (MRHD) are within those of the referenced drug. All excipients in the proposed formulation are within levels of other approved products. The (b) (4) impurity specification is consistent with FDA's finding of safety and effectiveness for the referenced drug, while all other impurities are within acceptable levels. Additionally, a 28-dog repeat dose toxicity study supports the new formulation of G-ER. Therefore from the non-clinical pharmacology/toxicology perspective, this NDA may be approved.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the clinical pharmacology, based on the clinical pharmacology review team's analysis and conclusions, has been reproduced from pages 6 to 8 of Dr. Fields' review:

> Six Clinical Pharmacology studies were submitted with the NDA and include:
>
> - Relative bioavailability G-ER vs. IR (studies 81-0040, 81-0049, and 81-0050).
> - Dosage-form proportionality (2x300 mg vs. 1x600 mg; Study 81-0040)
> - Dose-proportionality (range 600 to 2400 mg; Study 81-0044)
> - Food effect (Study 81-0048)
> - Single and Multiple dosing pharmacokinetics of G-ER (Study 81-0049)
> - Modeling and simulation for dosing in renally impaired patients (Reports 85-0009 and 85-0010)
>
> Since the extended-release characteristics of the G-ER formulation are dependent upon its consumption with food, all PK studies were conducted in the fed state.
>
> During drug development, the Applicant studied three formulations of G-ER. A pilot formulation (pilot relative bioavailability study), a phase 2 formulation (dose-proportionality, dosage-form proportionality, and phase 2 clinical studies), and a phase 3 formulation (relative bioavailability, single dose, and multiple dose PK study, food effect study, and the two phase 3 clinical studies). The phase 3 and to-be-marketed formulations

are exactly the same except for color and debossing for 600 mg and debossing for 300 mg.

G-ER 1800 mg administered once-daily demonstrated comparable BA to Neurontin, administered 600 mg three times daily. G-ER, dosed with the evening meal, has similar AUC and Cmax values as that of IR regimen. After multiple dosing, G-ER showed no accumulation and steady state was reached after 2 days. The trough concentrations are about 45% lower with G-ER tablets than with Neurontin. With respect to percent degree of fluctuation and percent 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). The implication of the fluctuation and swing are discussed below in the summary of the Biopharmaceutics review.

Two 300 mg and one 600 mg G-ER tablets evaluated with phase 2 formulation were shown to have equivalent exposure (study 81-0044). This is not the to-be-marketed formulation, so this information does not contribute to support for approval of G-ER. There was no dosage-form proportionality study conducted for the commercial formulation.

Food has only a slight effect on the rate and extent of absorption of IR gabapentin (14% increase in AUC and Cmax) 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. All 6 PK studies, one Phase 2 and two Phase 3 studies were performed in the fed state. The effect of food, specifically fat content, 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.

Single oral doses of G-ER from 600 mg to 2400 mg resulted in less than proportional increases in both AUC and Cmax. Similar to IR gabapentin, the bioavailability of G-ER 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.

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, renal impairment will increase systemic exposure to the drug. The Applicant did not evaluate the impact of renal impairment on gabapentin pharmacokinetics after administration of G-ER formulation. However they addressed this issue using prior knowledge of the 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 Applicant acceptable in the patients with creatinine clearance of > 30 mL/min and not acceptable for the patients with creatinine clearance range of 15-30 mL/min. For details regarding the models and the Applicant's recommendations see Dr. Bhattaram's review.

Based on the simulations, the review team proposes the following dosing of G-ER in renally impaired patients based on creatinine clearance:

Table 1: Recommended Dosing in Renally Impaired Patients

Once-daily dosing	
Creatinine Clearance (mL/min)	G-ER Dose (once daily with evening meal)
≥60	1800 mg
30 – 60	600 mg to 1800 mg
< 30	G-ER should not be administered
In patients receiving hemodialysis	G-ER should not be administered

Source: adapted from Dr. Bhattaram's review

Clinical Pharmacology Conclusions

Data characterizing the single and multiple-dose PK, relative bioavailability to the reference drug, Neurontin, and the effect of food for the phase 3 formulation, provides sufficient information to approve G-ER from the PK perspective. In addition, since the phase 3 formulation was used in the Phase 3 clinical trials, lack of dose-proportionality data for the phase 3 formulation is not of critical concern. Although there is no PK data available for the phase 3/to-be-marketed 300mg dosage tablet, its use in the Phase 3 clinical trials provides adequate support for its approval from the clinical pharmacology perspective.

As noted above in Section 2, Drs. Suarez Sharp and Marroum concluded that there were deficiencies in this application that should preclude its approval. The following review summary and conclusions have been reproduced from pages 1 to 4 of Dr. Suarez Sharp's review:

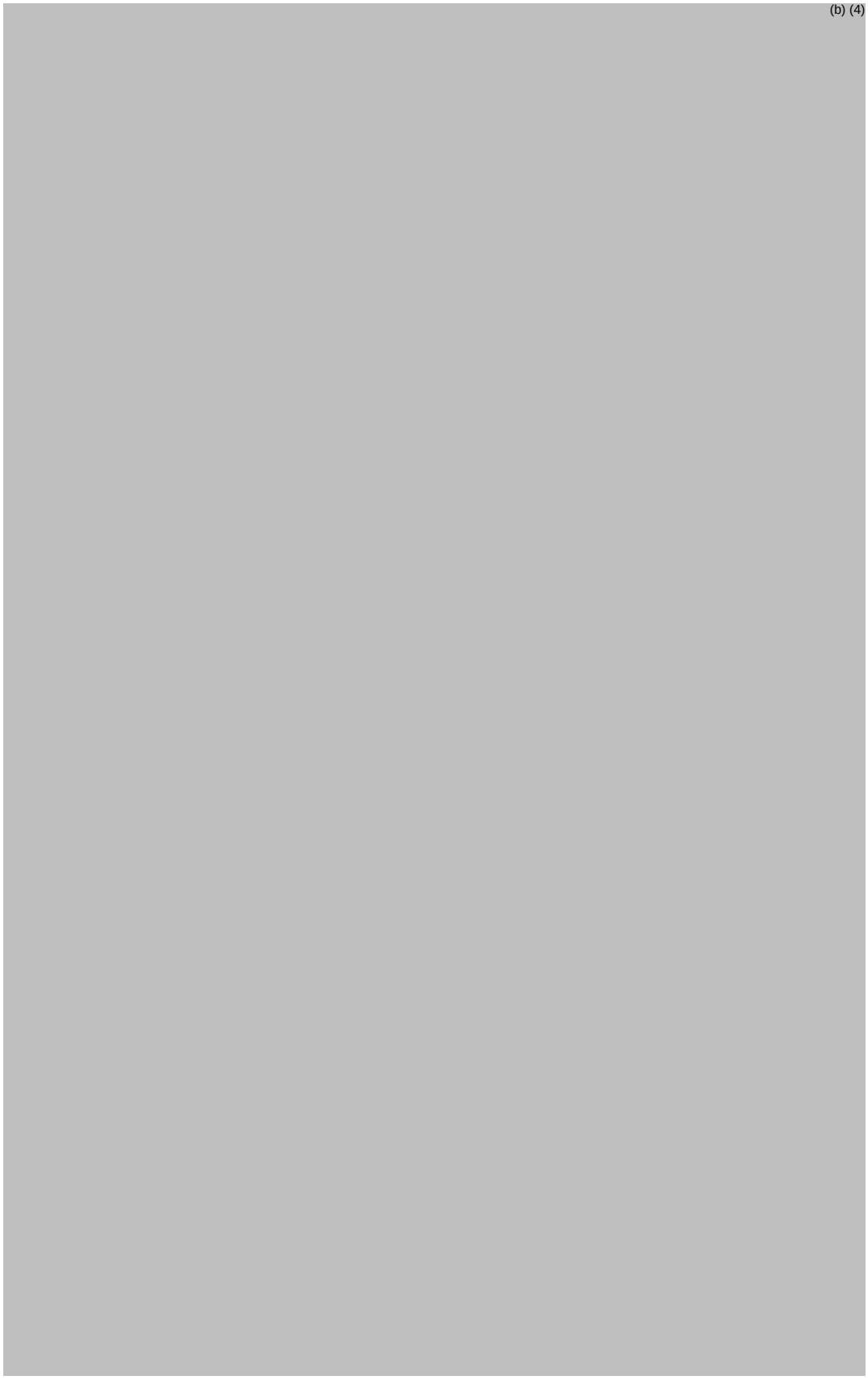
REVIEW SUMMARY:

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.

(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.
   c.
   d.
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.

The applicant proposed new dissolution specifications and the review team found them to be acceptable. In regard to the concerns raised regarding the 300 mg tablet, both the clinical pharmacology and the clinical review teams have concluded that, even in the absence of pharmacokinetic data supporting bioequivalence, the fact that this dosage is used solely for titration and that it was used successfully in this manner in the clinical studies are adequate to support its approval for use in titration. I concur with this conclusion.

I also concur with the clinical team regarding the food effect's impact on approvability. The following summarizes the clinical review team's conclusions regarding the high variability in absorption of this product due to the unusual effect of food on this formulation (reproduced from page 27 of Dr. Fields' review):

> The high fluctuation index would not be expected to affect safety, since the higher fluctuation for G-ER relates to the minimum concentrations (trough levels) detected and not the maximum plasma concentrations. In terms of systemic exposure and the type of meal consumed, the highest exposure is obtained with consumption of a high fat meal, and decreases with decreasing fat content of the meal. The Applicant has provided data that demonstrates systemic exposure for G-ER 1800mg taken with a high fat meal is comparable to systemic exposure following treatment with Neurontin 3X600mg in a fed state.[1] Therefore, the concern with the variability in fat content will not likely impact safety, as meals with lower fat content will result in a lower systemic exposure to gabapentin.
>
> It is certainly possible that the fluctuation in systemic exposure and the fat-dependent variability of absorption could affect the efficacy of G-ER. If the approval of G-ER rested solely on pharmacokinetic and biopharmaceutic findings, these issues could preclude approval. However, an adequate and well-controlled clinical trial was conducted in patients with PHN in which efficacy was demonstrated. In addition, the therapeutic window for gabapentin as an analgesic may not be as narrow as when it is used for the treatment of epilepsy. There is, in fact, no data regarding the pharmacokinetic/pharmacodynamic relationship of gabapentin for the treatment of PHN. Since G-ER did demonstrate efficacy in the clinical trial, where the fat content of the meals consumed with G-ER was not controlled, it appears that despite the fluctuations in systemic exposure and fat-dependent variability of absorption, G-ER was efficacious in the treatment of PHN in the clinical study population.

Finally, I concur with the biopharmaceutics and clinical review teams regarding the designation of Gralise as an extended-release product. The formulation does not meet the regulatory requirements for a product designed to be extended release (b) (4) However, the product did demonstrate efficacy with once daily dosing, so that dosing information is acceptable and appropriate for the Dosing and Administration section of the package insert.

[1] It should be noted that there is no significant food effect on the PK of Neurontin.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The applicant submitted the results of three efficacy trials, one Phase 2 and two Phase 3 studies. Both the Phase 2 study and one of the Phase 3 studies failed to demonstrate a statistically significant treatment effect. The failed studies were of similar design to the successful trial, Study 62. The clinical and statistical reviewers have addressed the full efficacy program in their reviews. I will focus only on Study 62, as the division only required a single, successful, adequate and well-controlled study for this application.

Study 62 was a double-blind, placebo-controlled, parallel-group trial that compared treatment with Gralise 1800 mg once daily with placebo. A two-week titration period was included to reach the targeted dose, which was to be taken with the evening meal for which the fat and caloric content were not specified. Subjects must have suffered from PHN for at least 6 months and were required to have an average daily pain score of 4 or greater on an 11-point Likert scale from screening through randomization for entry into the double-blind period. Certain concomitant analgesics were allowed to be continued at a stable dose, including SSRIs tricyclic antidepressants, acetaminophen, aspirin for cardiac prophylaxis, and NSAIDs if prescribed for conditions other than the PHN. Subjects who were previously unresponsive to gabapentin at doses of 1200 mg or greater and subjects with a creatinine clearance of less than 50 mL/minute were excluded. The trial continued for 8 weeks at the 1800 mg dose. The drug was then tapered to off over one week at the end of treatment. This was a multinational study with 57% of the subject population in the U.S.

The primary outcome measure was the change in average daily pain intensity score from the baseline week to the final week of the study. Missing data was imputed using Baseline Observation Carried Forward. Secondary endpoints included the Patient Global Impression of Change, Clinician Global Impression of Change and Daily Sleep Interference Score. As is frequently seen in analgesic clinical trials, there was a differential in dropout rates in the ITT population, with a higher percentage of dropouts due to adverse events in the Gralise-treated subjects and a higher percentage of dropouts due to lack of efficacy in the placebo-treated subjects. The following table reproduced from page 13 of Dr. Fields' review summarizes the primary outcome analysis results:

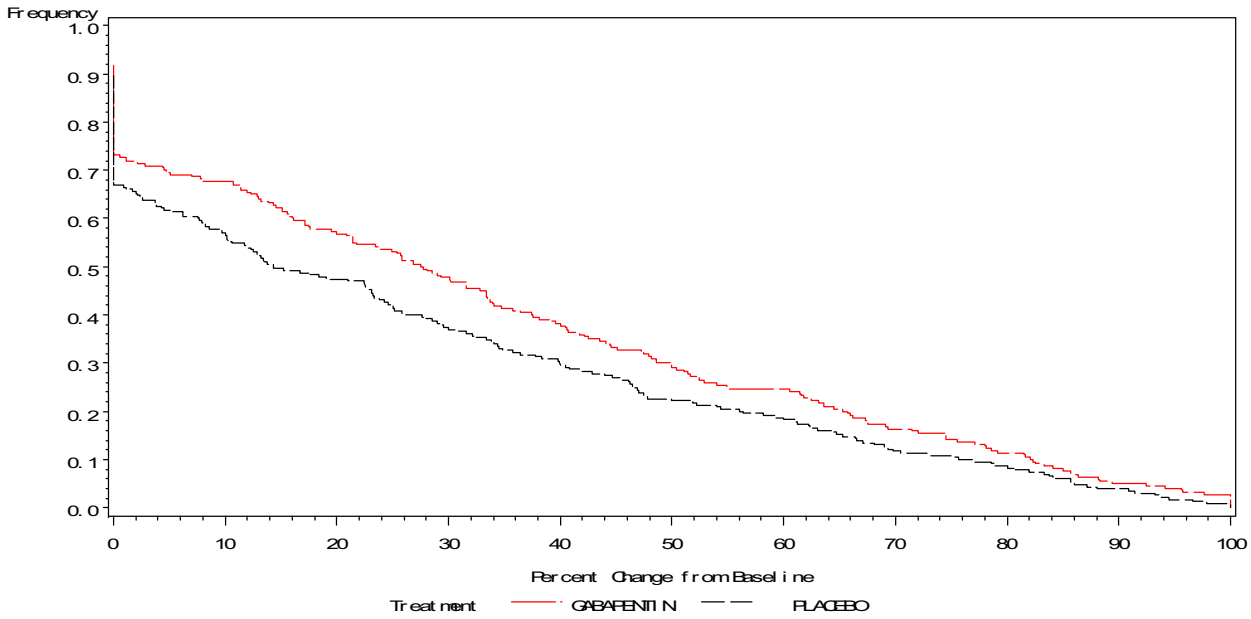
Analysis of BOCF Average Daily Pain Score: ITT Population

Average Daily Pain Score	Gabapentin ER 1800 mg (n = 220)	Placebo (n = 230)	G-ER vs. Placebo p-value
Baseline:			
Mean (SD)	6.6 (1.4)	6.5 (1.4)	
95% CI	(6.40, 6.77)	(6.37, 6.73)	
p-value (vs. Placebo)[1]			0.783
Endpoint:			
Mean (SD)	4.5 (2.4)	4.9 (2.3)	
Change from Baseline to Endpoint:			
Mean (SD)	-2.1 (2.1)	-1.6 (2.0)	
LS Mean (SEM)	-2.12 (0.17)	-1.63 (0.16)	
95% CI	(-2.44, -1.79)	(-1.95, -1.30)	
Gabapentin ER minus Placebo			
LS Mean Difference (SEM)	-0.49 (0.20)		
95% CI for Difference	(-0.88, -0.11)		
p-value (vs. Placebo)[2]			0.0125

Source: Applicant's Clinical Study Report 81-0062 p. 66

Dr. Kim was able to replicate these results. He also conducted a continuous responder analysis and the graph below, reproduced from page 14 of Dr. Fields' review, summarizes the results of that analysis:

Continuous Responder Curves: Study 81-0062



Source: Dr. Kim's Statistical Review

The difference between the two treatments in this analysis resulted in a p-value of 0.039 when a van der Waerden test was performed. Dr. Kim also performed an analysis to examine whether the use of concomitant analgesics had an impact on the primary outcome results as a slightly higher percentage of Gralise-treated subjects used concomitant analgesics compared to the placebo-treated subjects. He found that this differential did not affect the outcome. The results for the secondary endpoints were generally supportive of the primary outcome analysis results.

8. Safety

The following table, reproduced from page 19 of Dr. Fields' review, summarizes the extent of exposure to Gralise in the Phase 2 and 3 studies:

Extent of Exposure in Analysis Set B

Number of patients who received treatment	G-ER 1800 mg QD, N (%)	G-ER 1800 mg (AM/PM), N (%)	Placebo; N (%)	Total; N (%)
Total	413 (100%)	187 (100%)	415 (100%)	1015 (100%)
≥1 week	403 (97.6%)	179 (95.7%)	407 (98.1%)	989 (97.4%)
≥4 weeks	382 (92.5%)	161 (86.1%)	376 (90.6%)	919 (90.5%)
≥ 10 weeks	298 (72.2%)	97 (51.9%)	284 (68.4%)	679 (66.9%)

Source: NDA Submission, Clinical Overview, p. 35

There was one death (in the Phase 2 study) in an elderly woman with a history of coronary artery disease. She died of cardiac arrest on Day 13 of treatment with Gralise. Drs. Jiang and Fields concurred with the applicant's assessment that the death was highly unlikely to have been due to the drug, particularly as gabapentin has been widely used and is not associated with cardiac disease or cardiac death. There were 32 serious adverse events reported, with pneumonia being the only one reported in more than one subject receiving Gralise. Upon review of the pneumonia cases, Drs. Jiang and Fields concluded that they were not related to study drug exposure. The most common adverse events resulting in discontinuation in the Gralise-treated subjects were dizziness and nausea, both known effects of gabapentin. The common treatment emergent adverse events were also those known to occur with gabapentin treatment and included: dizziness, somnolence, headache, peripheral edema, dry mouth, constipation and nausea. There was a single serious adverse event of hypersensitivity in an open-label extension study that was considered by the investigator and Dr. Jiang to be related to study drug exposure.

Dr. Jiang also performed an analysis of the gastrointestinal adverse events to assess whether the gastric-retentive formulation might result in any obstructions. The table below, reproduced from page 24 of Dr. Fields' review, summarizes the gastrointestinal events that occurred in the Phase 2 and 3 studies:

Gastrointestinal TEAEs in Phase 2 and 3 PHN Studies

	G-ER Daily N 413 N (%)	G-ER BID N 187 N (%)	Placebo N 415 N (%)	Total N 1015 N (%)
Abdominal distension	0 (0)	1 (0.5)	3 (0.7)	4 (0.3)
Abdominal pain*	5 (1.2)	1 (0.5)	8 (1.9)	14 (1.3)
Constipation	7 (1.7)	7 (3.7)	1 (0.2)	15 (1.5)
Diarrhea	14 (3.4)	7 (3.7)	15 (3.1)	34 (3.3)
Dry mouth	14 (3.4)	8 (4.3)	7 (1.7)	29 (2.9)
Dyspepsia	6 (1.5)	2 (1.1)	5 (1.2)	13 (1.3)
Nausea	16 (3.9)	9 (4.8)	18 (4.3)	43 (4.2)
Vomiting	5 (1.2)	3 (1.6)	5 (1.2)	13 (1.3)

* combined abdominal pain and abdominal pain (upper)
Source: Dr. Jiang's review

There did not appear to be any increase in obstruction, distension, constipation or other potentially concerning events. There were no clinically concerning laboratory abnormalities or vital sign changes in the subjects exposed to Gralise.

9. Advisory Committee Meeting

This application was not taken to advisory committee as it is for a simple reformulation of a well known drug substance, and no unusual or concerning efficacy or safety concerns arose during the review period.

10. Pediatrics

The following has been reproduced from page 25 of Dr. Fields' review:

> The Applicant submitted a Pediatric Plan with the NDA requesting a waiver of studies for PHN in the pediatric population because it would be impracticable to conduct studies given the essential absence of the condition in pediatric patients. The waiver request was presented to the Pediatric Research Committee on November 3, 2010, at which time the request was granted.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Although the review team and the applicant have reached agreement on the product labeling, it should be noted that the removal of any and all language referencing (b) (4) was undertaken by the Agency. While the applicant agreed to this change, they did so reluctantly.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The applicant has provided sufficient data in this application to support a finding of safety and efficacy for this new formulation of gabapentin. While Gralise was developed as an extended-release formulation, (b) (4) Therefore, Gralise cannot be labeled or promoted as an "extended-release product." Nevertheless, the clinical studies performed with Gralise, during which the product was taken with a meal but without specific directions for the caloric or fat content of the meal, demonstrated that the product remains effective over a 24-hour interval. Therefore, it is acceptable for the Dosing and Administration section to include instructions for once daily dosing. There were no new safety findings or concerning differences in the safety profile of Gralise compared to gabapentin immediate-release formulations demonstrated in the clinical studies.

  - Postmarketing Risk Evaluation and Management Strategies

  The following has been reproduced from page 28 of Dr. Fields' review:

  > Since the approval of Neurontin in 1993, the Agency has become aware of safety information indicating an increased risk of suicidal thoughts and behavior with antiepileptic drugs (AEDs). A MedGuide only REMS that included the AED class MedGuide was approved for Neurontin on October 11, 2010. Since Gabapentin-ER contains the same active moiety and is in the AED class, a similar MedGuide only REMS is required for approval of this product.
  >
  > The Applicant has submitted a REMS that includes the AED class MedGuide and the required timeline for the REMS assessments.

  The REMS has been reviewed by the review team and found to be acceptable.

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

/s/

BOB A RAPPAPORT
01/28/2011