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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 17, 2010
From	Ellen Fields, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-544
Applicant	Abbott Products, Inc.
Date of Submission	March 30, 2010
PDUFA Goal Date	January 30, 2011
Proprietary Name / Established (USAN) names	Gralise/Gabapentin ER
Dosage forms / Strength	Tablets/300mg and 600mg
Proposed Indication(s)	Treatment of Postherpetic Neuralgia
Recommended:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Reviewers**
Primary Medical Officer Review	Timothy Jiang, MD, PhD
Statistical Reviews	Youngman Kim, PhD, Dionne Price, PhD
Pharmacology Toxicology Reviews	Armaghan Emami, PhD, Adam Wasserman, PhD
Clinical Pharmacology	Suresh Naraharisetti PhD, Suresh Doddapaneni, PhD
Biopharmaceutics	Sandra Suarez Sharp, PhD, Patrick Marroum, PhD
CMC	Yong Hu, PhD, Prasad Peri, PhD
DSI	Susan Leibenhaut, MD,
OSE/DMEPA	Judy Park, PharmD, Carol Holquist, RPh
OSE/DRISK	Shawna Hutchins, MPH, RN
OSE/DPVII	Martin Pollock, Pharm.D., Lauren Choi, Pharm.D.

Cross Discipline Team Leader Review Template

1. Introduction

This New Drug Application was submitted by Abbott Products (henceforth referred to as the Applicant) for Gabapentin Extended Release (G-ER) Tablets for the indication of the management of postherpetic neuralgia (PHN). It was submitted under 505(b)(2) of the FD&C Act, and as such the Applicant has relied on the Agency's previous findings of efficacy and safety for Neurontin (Gabapentin immediate release tablets, NDA's 20-129, 20-235, 20-882, 21-397, 21-423, and 21-424) to support this application.

2. Background

The Applicant developed G-ER tablets as an extended release, gastric-retentive formulation containing gabapentin, intended for once daily administration of 1800mg for the management of PHN in adults. According to the Applicant, the nature of the formulation is such 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 the drug is gradually released over approximately 8-10 hours in the upper gastrointestinal (UGI) tract where gabapentin is best absorbed. This differs from conventional controlled-release oral dosage forms that release drug over an extended period of time, but pass through the UGI tract in a short period of time. The Applicant maintains that the slow release of gabapentin in the UGI tract with this formulation allows for greater absorption of the drug. Similar gastric-retentive formulations marketed as Glumetza (metformin HCL extended release tablets) and Proquin XR (ciprofloxacin HCl) have been previously approved by the Agency.

Immediate-release gabapentin (Neurontin) was originally approved in December, 1993 as adjunctive therapy for the treatment of partial seizures, and was subsequently approved for the management of PHN in adults in May, 2002 (NDA 21-424). The approved dose for Neurontin in adults with PHN is 1800mg/day, administered in three equally divided doses. According to the Neurontin label, doses above 1800mg do not provide additional efficacy. The most common adverse events associated with Neurontin administration are dizziness, somnolence, and peripheral edema. The Applicant states in their submission that G-ER was developed on the premise that a once or twice daily formulation would improve patient compliance, and when given in the evening, would enhance the relief of nighttime pain, and thereby improve sleep.

The Agency provided guidance to the Applicant regarding the development of G-ER during End-of-Phase 2 and pre-NDA meetings. One positive adequate and well-controlled clinical efficacy trial in patients with PHN was sufficient, given that the Applicant was relying in part on previous findings of efficacy and safety for Neurontin for this 505(b)(2) application. A safety database of 300 to 500 patients was also required for approval.

The Applicant's pharmacokinetic development program included six clinical pharmacokinetic studies in healthy volunteers in the fed state, and two modeling and simulation studies. The clinical development program included one five-week Phase 2 proof-of-concept trial, two 11-

week (8 weeks of double-blind treatment) Phase 3 clinical trials, and one open-label extension study lasting an additional 13 weeks.

During the review cycle, the Biopharmaceutics team raised several issues regarding the formulation that will be discussed in detail in this review.

3. CMC/Device

This section summarizes the CMC review that was conducted by Yong Hu, Ph.D., with secondary concurrence from Prasad Peri, Ph.D.

The drug product is an extended-release oral tablet containing 300mg and 600mg of gabapentin. Of note, the Biopharmaceutics team has recommended that the product not be classified as an extended-release product (b) (4)

The tablets are targeted to deliver approximately 90% of the total daily dose of gabapentin over approximately 10 hours to the UGI tract. Gastric retention of the tablets is necessary for the delivery of the drug to the UGI tract over an extended period of time. The Applicant states that when administered with a meal, the tablet swells to the size which promotes gastric retention. 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)

There is a difference between the Phase3/registration stability batches, and the commercial product that includes the deboss (Depomed vs. SLV) and coat color (white vs. beige) for the 600mg tablet, and deboss only (Depomed vs. SLV) for the 300mg tablet. Since the tablet (b) (4) and there is no manufacturing process change from Phase 3 to commercial manufacturing, these changes are considered minor. 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 drug substance is freely soluble in water and the solubility is weakly dependently on the solution pH. The major degradation product is [redacted], thus, particle size specification has not been proposed by the Applicant for the drug substance. Particle size is said to be controlled by the supplier's internal specification. No data in the NDA supports the applicant's claim [redacted]
An information request was sent to the Applicant on December 3, 2010 requesting a particle size specification for the drug substance. The Applicant responded on December 7, 2010, and the CMC review team found the response acceptable.

The primary drug substance supplier is [redacted], and the alternate supplier is [redacted]. All Phase3/registration stability batches were manufactured using [redacted] gabapentin. The Applicant must provide a comparison of particle size distribution for the drug substances from both suppliers.

The drug product is packaged in bottles and blister packs for pharmacy and physician (samples) distribution, using acceptable materials. The blister pack consists of different configurations to be used as starter kits, titration kits, and unit dose packaging.

A 24-month expiration is recommended for both strength tablets packaged in either bottles or blister packs. The tablets are to be stored at 25^{O}C with excursions permitted to 15^{O} to 30^{O} C.

Manufacturing facilities have been deemed acceptable by the Office of Compliance. The Applicant has been granted a categorical exclusion, therefore no environmental assessment is required.

The following information request was sent to the Applicant on December 3, 2010. The Applicant's response dated December 7, 2010 was found acceptable by the CMC review team and will be discussed in full by Dr. Hu in a second CMC review.

- **The acceptance limit for the total impurities in the drug product should be tightened to [redacted] based on the stability data of your drug product.**
- **You have not provided adequate information to justify the omission of particle size in your drug substance specification. Include particle size test (method and acceptance limits) in your drug substance specification for both the primary and alternate suppliers.**
- **Provide a comparison of the particle size distribution for the drug substance from the primary and alternate suppliers.**
- **In accordance with the ICH Q1D guideline with respect to bracketing in stability testing, we recommend that you test the product stability in the bottle configurations with the lowest and the highest headspace/volume ratio for each strength in your post-approval stability programs.**
- **Provide dimensional information and pictures of the phase 3 tablets before and after swelling in mSGF for 6-8 hours.**

From the CMC perspective, this NDA is approvable.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was conducted by Armaghan Emami, Ph.D., with secondary concurrence by Adam Wasserman, Ph.D. The following summarizes Dr. Emami's review.

The Applicant conducted a 28-day repeat dose toxicity study in Beagle dogs (80-0014) using G-ER tablets (similar in formulation to those used in the clinical studies and proposed for marketing) as well as including a separate Neurontin group for bridging purposes.

Gabapentin in the form of either G-ER tablet (at doses of 0, 600, 1200, or 2400 mg/day) or Neurontin® IR Tablets (comparative control article, at dose of 2400 mg/day) was administered orally to 3 beagle dogs/sex/group daily for 28 days. Decreases in RBC and hemoglobin were noted in some animals who received G-ER 2400mg/day, but not in the groups receiving Neurontin. Increased testicular weight was also observed in dogs receiving 2400mg G-ER only. There were no clear treatment-related histopathology findings observed in this study. However, Dr. Emami states in her review that the hematology effects and testicular weight values differences with G-ER compared to Neurontin are likely due to the excipients used and may be a formulation issue. Due to organ weight and hematology findings, a dose level of 1200 mg/day was considered to be the NOAEL for G-ER. At 1200 mg/day on day 28, the exposure (AUC 0-24) was 492.5 and 598.4 µg.hr/mL and Cmax was 32.8 and 41.7 µg/mL in males and females, respectively. The exposures to gabapentin after the administration of G-ER tablets at the NOAEL exceeds (by 3.9- fold for Cmax and 4.1-fold for AUC) the exposure in humans dosed once daily with three 600 mg G-ER tablets, or 1800 mg/day, at steady state.

[redacted] - also known as [redacted] is an identified impurity of the drug substance and the drug product. The Applicant reduced the specification for [redacted] from [redacted] which at the maximum total daily intake of 1800 mg G-ER would represent [redacted] mg/day of the [redacted] impurity. This specification is above the ICH3B guidance. The nonclinical study in dogs does not support the proposed [redacted] specification. However, in consultation with Janice Weiner in the Office of Regulatory Policy (ORP), the

(b) (4) impurity specification is consistent with FDA's finding of safety and effectiveness for Neurontin, the referenced drug for this application, and therefore additional studies are not needed to qualify the level of this impurity at the proposed specifications. The Applicant is currently conducting an Ames assay, an in vitro Chromosomal aberration assay and a 1 month general toxicity study in rats to qualify the impurity. It is not necessary to review these reports because of ORP's decision.

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 Clinical Pharmacology review was conducted by Suresh Naraharisetti, Ph.D, with secondary concurrence by Suresh Doddapaneni, Ph.D. The Pharmacometric review was conducted by Atul Bhattaram, Ph.D., with secondary concurrence by Yaning Wang, Ph.D. The following summarizes their reviews.

The exact mechanism of action of gabapentin is unclear, however its therapeutic action in 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 postsynaptic excitability. The general pharmacokinetic characteristics of the gabapentin moiety are described in the Neurontin label and will not be discussed here.

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 $C_{max.}$ 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.

The Biopharmaceutics review was conducted by Sandra Suarez Sharp, Ph.D., with secondary concurrence from Angelica Dorantes, Ph.D., and Patrick Marroum, Ph.D. The following is a summary of Dr. Sharp's review. She identified several issues that could impact the approvability of G-ER.

The Biopharmacuetics team was consulted for this NDA in order to review the IVIVC model, the dissolution methods and specifications (b) (4), and the in vitro alcohol interaction study.

(b) (4)

(b) (4)

Proposed Dissolution Method and Specifications

Because the IVIVC model was found unacceptable, the proposed dissolution specifications are also not acceptable since at the 8 hour time point the percent variation is higher than (b) (4). Dr. Sharp recommends different dissolution specifications which are based on the mean in vitro dissolution profiles for G-ER tablets calculated from the available lot release/clinical data. The proposed dissolution method was found acceptable.

(b) (4)

(b) (4)

Dr. Sharp recommends that approval of this formulation be based on the results of an acceptable BE study or an approved IVIVC.

In Vitro Alcohol Interaction Study

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

The following comments were sent to the Applicant on December 3, 2010 in a Discipline Review Letter:

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

(b) (4)

(b) (4)

2. (b) (4)

(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:	
8 hours:	
12 hours:	

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.

Dr. Sharp also included the following comment in her review:

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.

At this writing, the responses from the Applicant to the Discipline Review letter are pending. Dr. Sharp will file an additional review following assessment of the Applicant's responses.

6. Clinical Microbiology

This section is not applicable to this application.

7. Clinical/Statistical- Efficacy

At meetings conducted between the Applicant and the Agency in December, 2005 (Type C meeting), August, 2006 (advice correspondence), and December, 2009 (pre-NDA meeting), the Agency conveyed that one positive adequate and well-controlled Phase 3 trial with eight weeks of double-blind treatment, would be sufficient for the demonstration of efficacy for G-ER for the management of PHN. Agreement was reached that the appropriate primary endpoint for this study would be the change from baseline to the end of double-blind treatment in daily pain score. In addition, the Agency informed the Applicant that a conservative imputation method such as BOCF, rather than LOCF, would be acceptable for the primary endpoint analysis, and that the conduct of a cumulative responder analysis where patients who dropped out for any reason would be considered treatment failures was strongly encouraged.

The Applicant submitted the results of one Phase 3 study (Study 62) as evidence of the efficacy of G-ER for the management of PHN. They also submitted results of two supporting studies, one Phase 2 proof-of concept study (Study 38), and an additional Phase 3 study (Study 45), both of which failed on their primary endpoint. All three studies were double-blind, placebo-controlled, parallel group designs, and all three included a one week period to establish a baseline score. To be eligible for randomization, subjects must have had an average daily pain score of 4 or more on the 0-10 point Likert numerical rating scale (0 no pain, 10 worst possible pain) at entry and average score of 4 or more for the baseline week at randomization and have recorded a score in their electronic diary on 4 or more of the 7 days. Randomization was at a 1:1 (G-ER:placebo) ratio for Study 62, and 1:1:1 (G-ER QD:G-ER BID: placebo) for studies 38 and 45.

Each of the three studies included a two week titration period to reach the target dose of 1800mg per day to be given with a meal. The fat and calorie content of the meal was not specified. Inclusion and exclusion criteria were similar for all three studies; All were conducted in adult patients ages 18 years and older in whom postherpetic neuralgia pain had been present for at least 3 months in studies 38 and 45, and at least 6 months in study 62. Concomitant medications permitted at a stable dose during the treatment period included antidepressants except selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), acetaminophen (APAP) up to 4 grams per day, aspirin (ASA) for cardiac prophylaxis, and nonsteroidal anti-inflammatory drugs (NSAIDS) if used to treat conditions other than PHN. Patients who had previously been unresponsive to treatment with gabapentin at daily doses of 1200mg or greater were excluded, as were patients with a creatinine clearance of <50mL/min. The Phase 2 study had a total efficacy treatment period of 4 weeks, and both Phase 3 studies had double-blind duration of treatment that included two weeks of titration followed by 8 weeks at the target dose of 1800 mg per day. Dose titration was started at 300mg and increased to 1800mg over the two week titration period. The Phase 2 study and Phase 3 Study 45 included once daily and asymmetric BID (600mg in AM, 1200mg in PM) dosing of G-ER, and Phase 3 Study 62 included only once daily dosing. One week at the end of treatment was allowed for dose tapering. Patients entered their average daily pain intensity scores each morning in an electronic diary. The primary endpoint for all studies was the change in average daily pain score from baseline week to the final week of treatment. An unmodified baseline observation carried forward (BOCF) method of imputation was applied for both Phase 3 studies, and last observation carried forward (LOCF) was used for the Phase 2

study. Secondary endpoints included the Patient global impression of change (PGIC), Clinician global impression of change (CGIC), and the daily sleep interference score (DSI).

The results of Study 62 will be discussed below. Since Studies 38 and 45 did not meet their primary efficacy endpoints, they will not be discussed in this review. Please refer to Dr. Timothy Jiang's review for details regarding those studies. The following is a summary of Dr. Jiang's review of Study 62, and the statistical analyses conducted by Dr. Youngman Kim.

Study 62, A Phase 3 Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Once-Daily Gabapentin Extended Release (G-ER) Tablets in the Treatment of Patients with Postherpetic Neuralgia, was conducted at 89 study sites in the United States (57% of study population), Russia (36%) and Argentina (7%). A total of 452 patients were randomized to either G-ER 1800mg once daily with the evening meal or placebo at a 1:1 ratio. Of the 221 patients included in the ITT population who received G-ER, 185 completed the study; of the 231 patients who received placebo in the ITT population, 192 completed the study. The following table from Dr. Jiang's review shows the reasons for dropout from the study. As expected, more patients who received study drug dropped out due to adverse events (AEs), while a higher percentage who received placebo discontinued due to lack of efficacy. The overall dropout rate was similar for both groups (16-17%). A total of 84% of randomized patients completed the study.

Table 2: Patient Disposition, Study 62

	G-ER 1800 mg Daily N 221(%)	Placebo N 231 (%)	Total N 452 (%)
Dropout	36 (16)	39 (17)	75 (17)
AE	19 (53)	8 (21)	27 (36)
Lack of efficacy	7 (19)	12 (31)	19 (25)
Protocol violation	2 (6)	2 (5)	4 (5)
Lost to follow-up	0	1 (3)	1 (1)
Death	0	1 (3)	1 (1)
W/D of consent	4 (11)	9 (23)	13 (17)
Others	4 (11)	6 (15)	10 (13)

Source: Modified from Applicant's submission (PN-81-0062 Clinical Study Report, page 56)

The demographics and baseline characteristics were similar for both treatment groups. The majority of the patients were over 65 years of age (mean age 65.6), female (62%), and Caucasian (89%), and the mean baseline average daily pain scores were essentially equivalent (6.6 G-ER vs. 6.5 placebo). The two most common locations for the neuropathic pain were posterior and anterior torso, which together made up approximately 85% of patients, and was similar between treatment groups. There were no protocol violations reported that would be expected to impact the efficacy findings of the study.

The primary efficacy endpoint was the mean change in average daily pain (ADP) scores from the baseline week to the final week of the efficacy treatment period for patients treated with G-ER compared to placebo. The Applicant employed a BOCF imputation for missing data, using analysis of covariance (ANCOVA) as the statistical model with treatment and center as

factors, and baseline score as covariate. The primary analysis set (ITT population) included all randomized subjects who received at least one dose of study medication. The study was powered at 90% to detect a treatment effect of -0.4 units on the Likert 11-point scale.

Three key secondary endpoints were analyzed using adjustments for multiplicity, and included the PGIC, CGIC, and DSI. If either the PGIC or CGIC were significant at the 0.25 level, then DSI was to be tested at the 0.05 level.

Table 3,taken from the submission, shows the Applicant's analysis of the primary endpoint ,which resulted in a statistically significant p-value.

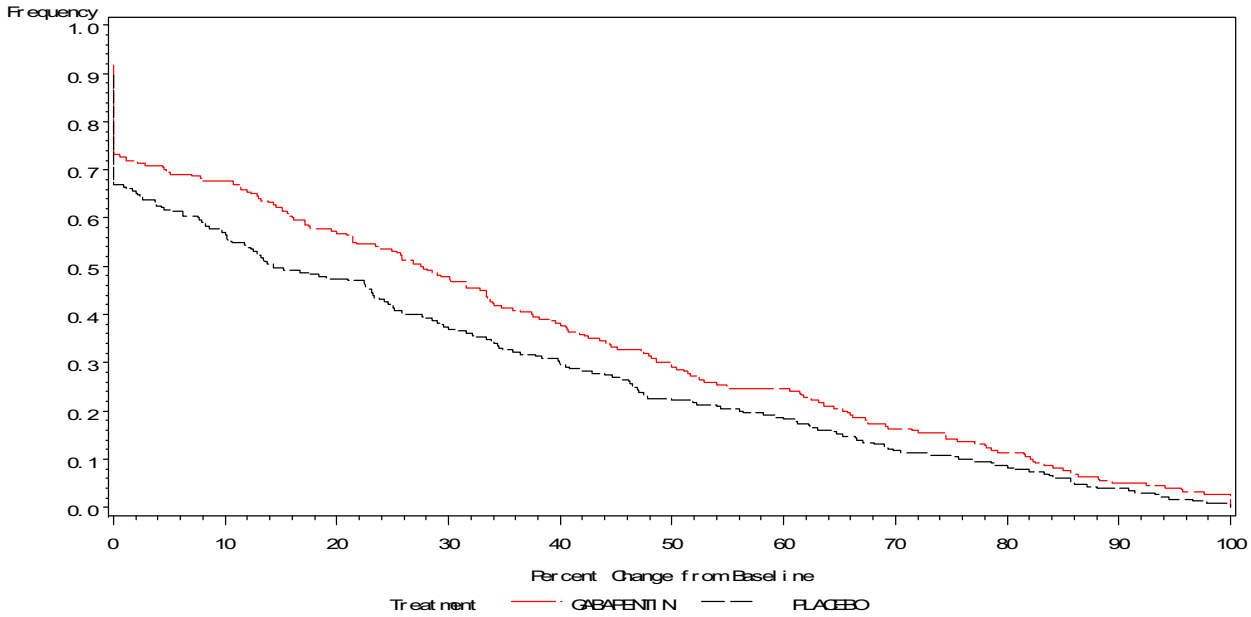
Table 3: Analysis of BOCF Average Daily Pain Score: ITT Population

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 the Applicant's primary analysis. He also conducted a continuous responder analysis as supportive evidence of efficacy of G-ER, where dropouts for any reason were considered treatment failures. The figure below taken from Dr. Kim's review uses the Applicant's data, resulting in a P-value of 0.039 based on van der Waerden test.

Figure 1: Continuous Responder Curves: Study 81-0062



Source: Dr. Kim's Statistical Review

Dr. Kim also conducted a sensitivity analysis on the primary endpoint including the use of rescue medication in the analysis. The P-value was calculated using an ANCOVA model with terms for treatment, center, and baseline score as covariate. It is of note that a slightly higher percentage of patients treated with G-ER (5.9%) received rescue medication during the treatment period compared to placebo patients (4.8%). However, when the primary endpoint was reanalyzed counting patients who took rescue as treatment failures, the P-value was statistically significant in favor of the G-ER group.

Table 4: Reviewer Sensitivity Analysis of Primary Endpoint:
Patients Taking Rescue Medication Considered Treatment Failures

ADP	G-ER 1800mg QD (N 220)	Placebo (N 230)
LS Means (SE)	-2.0 (0.17)	-1.6 (0.16)
Difference from placebo (SE) 95% CI	-0.4 (0.19) (-0.8, -0.0)	
P-value*	0.030	

Source: Dr. Kim's statistical review

Three secondary endpoints were analyzed based on a prespecified analysis that included adjustments for multiplicity.

1. The proportion of patients who were categorized as "very much" or "much improved" in Patient Global Impression of Change (PGIC)

2. The proportion of patients who were categorized as "very much" or "much improved" in Clinical Global Impression of Change (CGIC)

3. The mean change in BOCF average daily sleep interference (ADSI) score from baseline to the final week of the efficacy treatment period, evaluated from the daily sleep entry in the electronic diaries which were assessed on an 11-point numeric rating scale ranging from 0 (pain does not interfere with sleep) to 10 (pain completely interferes with sleep)

According to the Applicant's prespecified statistical analysis plan, PGIC and CGIC were tested simultaneously, and if either was significant at the p 0.025 level, the third endpoint, ADSI was to be analyzed at the p .05 level.

The summary tables below from Dr. Kim's review illustrate the results of the analyses of the secondary endpoints. Based on the sequential testing procedure, significance was not achieved for the secondary endpoints. However, all trended numerically in favor of G-ER, and CGIC narrowly missed statistical significance at P .027. Since both PGIC and CGIC failed to meet statistical significance, the analysis of ADSI, despite the fact it was statistically significant, is for descriptive purposes only.

Table 5: Applicant's Analysis of Secondary Efficacy Variable: PGIC

PGIC	G-ER 1800mg QD (N 220)	Placebo (N 230)
Very Much or Much Improved at Endpoint	94 (43%)	77 (34%)
Difference from placebo	9%	
P-value*	0.043	

P-value calculated from chi-square test. Not significant at 2.5% level.
Source: Dr. Kim's statistical review

Table 6: Applicant's Analysis of Secondary Efficacy Variable: CGIC

CGIC	G-ER 1800mg QD (N 220)	Placebo (N 230)
Very Much or Much Improved at Endpoint	97 (44%)	78 (34%)
Difference from placebo	10%	
P-value*	0.027	

P-value calculated from chi-square test. Not significant at 2.5% level.
Source: Dr. Kim's statistical review

Table 7: Applicant's Analysis of Secondary Efficacy Variable: ADSI

ADSI	G-ER 1800mg QD (N 220)	Placebo (N 230)
LS Means (SE) from Baseline to Week 11*	-2.3 (0.16)	-1.6 (0.15)
Difference from placebo (SE) 95% CI	-0.7 (0.18) (-1.1, -0.4)	
P-value*	<0.001	

Presented only for descriptive purpose due to failure in sequential testing of first two secondary endpoints
P-value calculated from ANCOVA model with terms for treatment, center, and baseline score as covariate.
Source: Dr. Kim's statistical review

Additional exploratory secondary endpoints were assessed, however the analyses were not adjusted for multiple endpoints. Refer to Dr. Jiang's review for details regarding these endpoints.

Drs. Kim conducted exploratory subgroup analyses of the primary endpoint by country. It showed that only the US sites reached statistical significance for the primary endpoint, therefore overall efficacy for the primary analysis appears to come only from the US data. Furthermore, patients in Argentina showed a negative effect of G-ER compared to placebo, however considering the small proportion of the total study population from sites in Argentina (7%), this negative effect is not convincing. Refer to Dr. Kim's review for details regarding the analysis of the primary endpoint by country.

Subgroup analyses of the primary endpoint by age, race and gender showed no interaction by age or gender, but did suggest that G-ER demonstrates greater efficacy in non-whites (P

0.021). However, since approximately 90% of the patients were Caucasian, this finding may not be meaningful.

An exploratory comparison was conducted of the treatment effect based on the primary endpoint in this study and the treatment effect detected during the labeled Phase 3 trial for Neurontin. Using a conservative imputation method, the mean treatment effect in the Neurontin study was approximately 0.7 units (0-10 numerical rating scale), compared to a mean of approximately 0.5 units in this study. Details regarding this analysis can be found in Dr. Jiang's review. This comparison between studies has marked limitations, however it does show that the treatment effects for the Neurontin and G-ER appear to be similar in the two studies.

Summary of Efficacy Findings

Based on the reviews conducted by Drs. Jiang and Kim, the Applicant has demonstrated efficacy for G-ER for the treatment of pain associated with PHN in adult patients. Statistical significance was achieved for the primary endpoint, change in average daily pain score, over eight weeks of treatment in patients with PHN. The efficacy findings were driven by the US population which constituted 57% of the total study population. The prespecified secondary endpoints, CGIC, PGIC, and ADSI, did not reach statistical significance, however all trended in favor of G-ER. The Agency also conducted an exploratory continuous responder analysis, and an analysis of the primary endpoint taking rescue use into consideration, both of which further supported findings of efficacy for G-ER.

8. Safety

Dr. Jiang conducted a review of the safety data submitted by the Applicant. G-ER 1800mg once daily appeared to be relatively well tolerated among patients in the clinical trials. No new or unexpected safety signals were observed for G-ER, as compared with Neurontin. The following is a summary of Dr. Jiang's review.

The safety evaluation of G-ER in patients with PHN consisted of data from one Phase 2 study (81-0038), two Phase 3 studies (81-0045 and 81-062), and an open-label extension study (81-0052). The Applicant also submitted data from one Phase 2 study in patients with diabetic peripheral neuropathy (DPN). There were also six Phase 1 studies conducted in healthy volunteers. The safety data from the Phase 1 studies was reviewed by Dr. Jiang, and did not provide additional safety findings beyond that reported for the Phase 2 and 3 clinical trials.

The Applicant pooled the PHN data into two analysis sets. Analysis Set A included the two Phase 3 PHN trials, 45 and 62, and included only patients who received either placebo or G-ER 1800mg QD for 10 weeks (two weeks of titration plus eight weeks of double-blind treatment). The Applicant intended Set A to be used in labeling, as G-ER once daily is the intended marketed dose. Analysis Set B included all randomized patients who received at least one dose of study drug in the two Phase 3 trials in Analysis Set A plus the Phase 2 PHN trial in which patients received G-ER or placebo for four weeks (two weeks titration plus two weeks double-blind treatment). Details regarding the pooled datasets are shown in Table 8 below. From my perspective, the more inclusive Analysis Set B is the appropriate population to inform labeling, as it includes all subjects who received G-ER during the trials.

Data from the open-label extension study (52) was not pooled. This study provides data for an additional 14 weeks of treatment in patients with PHN who completed 10 weeks of treatment in Study 45. The safety data from this study will be discussed following the discussion of the double-blind safety data.

Table 8: Pooled Safety Datasets

Study	Phase	Dose Levels Included	Dosing Duration
Analysis Set A			
81-0045	3	1800 mg QD placebo	2 weeks titration, 8 weeks stable, 1-week taper
81-0062	3	1800 mg QD placebo	2 weeks titration, 8 weeks stable, 1-week taper
Analysis Set B			
81-0038	2	1800 mg QD 1800 mg asymmetric BID placebo	2 weeks titration, 2 weeks stable, 1-week taper
81-0045	3	1800 mg QD 1800 mg asymmetric BID placebo	2 weeks titration, 8 weeks stable, 1-week taper
81-0062	3	1800 mg QD placebo	2 weeks titration, 8 weeks stable, 1-week taper
BID = Twice daily, QD = Once daily.			

Source: Applicant's submission (Integrated Summary of Safety, page 18)

In contrast to the Applicant's focus on Analysis Set A, this review will focus on Analysis Set B, as it includes all patients with PHN who were randomized and received at least one dose of G-ER. However, any important differences between findings from Analysis Set A and B will be pointed out.

The following table from the submission shows the extent of exposure to G-ER in all randomized PHN patients in Phase 2 and 3 double-blind studies. A total of 413 patients were exposed to G-ER 1800mg QD, which satisfies the Agency's requirement for the safety database of 300 to 500 exposed patients.

Table 9: 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

The demographic characteristics for all treatment groups were similar; average age approximately 67 years, over 50% of patients were female, and over 85% were Caucasian.

One death was reported in a patient receiving G-ER in study 38 (Phase 2). She was a 73 year old woman who died of cardiac arrest 13 days after randomization. She had a history of PHN, subclavian aneurysm and hypertension, for which she was being treated with Hyzaar. At the time of her death she was still in the titration phase of the study and was receiving 600mg G-ER BID. The death was adjudicated by the Applicant as being due to severe coronary artery disease (CAD), and unrelated to study drug. Dr. Jiang reviewed the information provided by the Applicant and noted that information regarding the patients degree of preexisting CAD was not provided. However, since gabapentin, which has been marketed for many years, is not known to be associated with cardiac arrest, the likelihood that this death is associated with study drug is low.

A total of 32 serious adverse events (SAEs) were reported during the controlled PHN studies, 21 of which occurred in patients receiving either G-ER 1800mg QD or G-ER asymmetric BID dosing (600mg QAM, 1200QPM). The highest rate of SAEs was in the G-ER asymmetric BID group (4.8%), followed by G-ER QD and placebo at 2.7% each.

Pneumonia was the only SAE reported in more than one patient receiving G-ER. Four cases occurred in patients receiving G-ER 1800mg once daily, and none in patients receiving placebo. Dr. Jiang reviewed the cases in depth. All were diagnosed as community acquired pneumonia. All patients were elderly and had relevant comorbidities. I agree with Dr. Jiang's determination that the cases did not appear to be related to the study drug. Details regarding the cases are in the table below.

Table 10: Features of Pneumonia SAEs

Age	Major Co-morbidities	Community Acquired	ICU Admission	Days of Hospitalization
86	Hypertension hyperlipidemia	Yes	No	3
73	diabetes mellitus hypertension	Yes	No	2

82	COPD,CHF hypertension arrhythmia	Yes	Yes (Intubation)	13
81	Osteoarthritis cardiomegly pacemaker	Yes	No	3

Source: Dr. Jiang's review

One SAE of severe headache was considered by the Applicant to be related to treatment. Dr. Jiang reviewed the case and agreed with the Applicant's adjudication.

The disposition of patients from Analysis Set B is shown in the table below from the submission.

Table 11: Patient Disposition by Treatment Analysis Set B

	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Safety Population	**N=413**	**N=187**	**N=415**	**N=1015**
Discontinuation from study	**64 (15.5)**	**42 (22.5)**	**75 (18.1)**	**181 (17.8)**
Adverse Event	39 (60.9)	21 (50.0)	23 (30.7)	83 (45.9)
Lack of Efficacy	9 (14.1)	4 (9.5)	23 (30.7)	36 (19.9)
Protocol violation	2 (5.6)	2 (4.8)	5 (6.7)	9 (5.0)
Lost to Follow-up	1 (1.6)	4 (9.5)	2 (2.7)	7 (3.9)
Patient died	0 (0.0)	0 (0.0)	2 (2.7)	2 (1.1)
Patient withdrew consent	6 (9.4)	6 (14.3)	11 (14.7)	23 (12.7)
Other	7 (10.9)	5 (11.9)	9 (12.0)	21 (11.6)

Source: NDA Submission, ISS, p. 29

The highest overall rate of discontinuation from treatment occurred in the G-ER asymmetric BID dosing group at 22.5%. This was followed by placebo at 18% and G-ER 1800mg QD at 15.5%. The most common reason for discontinuation in both G-ER groups was an adverse event, followed by lack of efficacy and "patient withdrew consent". In the placebo group, an equal proportion of patients withdrew due to adverse event and lack of efficacy, which is unusual. More commonly in analgesic studies, the placebo patients most often withdraw from treatment due to lack of efficacy.

The following table from the submission shows the reasons for discontinuations due to adverse events reported for at least two patients in any treatment group in Analysis Set B. The most common AE associated with discontinuation in both G-ER treatment groups was dizziness, followed by nausea, both known to be associated with gabapentin treatment. The most common AE leading to discontinuation in the placebo group was nausea.

Table 12: Discontinuations due to Adverse Events Reported for Two or More Patients in Any Treatment Group: Analysis Set B

System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Analysis Set B	**N=413**	**N=187**	**N=415**	**N=1015**
Any AE	**39 (9.4)**	**21 (11.2)**	**26 (6.3)**	**86 (8.5)**
Cardiac disorders	**1 (0.2)**	**1 (0.5)**	**4 (1.0)**	**6 (0.6)**
Myocardial infarction	0 (0.0)	0 (0.0)	2 (0.5)	**2 (0.2)**
Ear and labyrinth disorders	**2 (0.5)**	**1 (0.5)**	**0 (0.0)**	**3 (0.3)**
Vertigo	2 (0.5)	1 (0.5)	0 (0.0)	3 (0.3)
Gastrointestinal disorders	**7 (1.7)**	**4 (2.1)**	**10 (2.4)**	**21 (2.1)**
Abdominal distension	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.2)
Diarrhoea	1 (0.2)	0 (0.0)	3 (0.7)	4 (0.4)
Nausea	3 (0.7)	3 (1.6)	4 (1.0)	10 (1.0)
General disorders and administration site conditions	**5 (1.2)**	**3 (1.6)**	**3 (0.7)**	**11 (1.1)**
Chest pain	2 (0.5)	0 (0.0)	1 (0.2)	3 (0.3)
Fatigue	0 (0.0)	1 (0.5)	2 (0.5)	3 (0.3)
Infections and Infestations	**7 (1.7)**	**0 (0.0)**	**2 (0.5)**	**9 (0.9)**
Pneumonia	3 (0.7)	0 (0.0)	0 (0.0)	3 (0.3)
Nervous system disorders	**14 (3.4)**	**13 (7.0)**	**7 (1.7)**	**34 (3.3)**
Dizziness	9 (2.2)	8 (4.3)	3 (0.7)	20 (2.0)
Headache	1 (0.2)	2 (1.1)	3 (0.7)	6 (0.6)
Lethargy	2 (0.5)	1 (0.5)	0 (0.0)	3 (0.3)
Somnolence	1 (0.2)	1 (0.5)	2 (0.5)	4 (0.4)
Psychiatric disorders	**2 (0.5)**	**4 (2.1)**	**0 (0.0)**	**6 (0.6)**
Confusional state	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)
Disorientation	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.2)
Respiratory, thoracic and mediastinal disorders	**3 (0.7)**	**0 (0.0)**	**1 (0.2)**	**4 (0.4)**
Dyspnoea	2 (0.5)	0 (0.0)	1 (0.2)	3 (0.3)

Source: Applicant's ISS, p. 59-62

Common treatment emergent adverse events (TEAEs) occurring in at least 1% of the patients in Analysis Set B are shown in the Applicant's table below. The most commonly reported TEAEs in patients treated with G-ER 1800mg QD were dizziness (12.3%), somnolence (5.1%), headache (4.8%), peripheral edema (4.4%), and nausea (3.9%). The most commonly reported TEAEs in patients treated with G-ER 1800 mg asymmetric BID were dizziness (13.9%), somnolence (7.0%), headache (4.8%), nausea (4.8%), dry mouth (4.3%), constipation, peripheral edema and diarrhea (3.7% each). For all of these commonly reported TEAEs, the incidence rate was higher in one or both of the G-ER treatment groups than in the placebo group, although not markedly so for the TEAEs of headache, nausea and diarrhea. The rates of common TEAEs reported for Analysis set A were similar to those for B.

Table 13: Common TEAEs in at Least 1% of Subjects in Analysis Set B

System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Analysis Set B	**N=413**	**N=187**	**N=415**	**N=1015**
Ear and labyrinth disorders				
Vertigo	6 (1.5)	1 (0.5)	2 (0.5)	9 (0.9)
Eye disorders				
Lacrimation increased	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.2)
Vision blurred	3 (0.7)	3 (1.6)	1 (0.2)	7 (0.7)
Gastrointestinal disorders				
Constipation	7 (1.7)	7 (3.7)	1 (0.2)	15 (1.5)
Diarrhoea	14 (3.4)	7 (3.7)	13 (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)
General disorders and administration site conditions				
Chest discomfort	1 (0.2)	3 (1.6)	1 (0.2)	5 (0.5)
Fatigue	9 (2.2)	5 (2.7)	6 (1.4)	20 (2.0)
Gait disturbance	5 (1.2)	2 (1.1)	0 (0.0)	7 (0.7)
Oedema peripheral	18 (4.4)	7 (3.7)	1 (0.2)	26 (2.6)
Infections and Infestations				
Gastroenteritis viral	2 (0.5)	3 (1.6)	1 (0.2)	6 (0.6)
Sinusitis	1 (0.2)	2 (1.1)	4 (1.0)	7 (0.7)
Upper respiratory tract infection	3 (0.7)	5 (2.7)	5 (1.2)	13 (1.3)
Urinary tract infection	7 (1.7)	2 (1.1)	2 (0.5)	11 (1.1)
Injury, poisoning and procedural complications				
Excoriation	0 (0.0)	2 (1.1)	1 (0.2)	3 (0.3)
Muscle strain	0 (0.0)	2 (1.1)	1 (0.2)	3 (0.3)
Investigations				
Weight increased	8 (1.9)	2 (1.1)	2 (0.5)	12 (1.2)
Metabolism and nutrition disorders				
Increased appetite	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.2)
Musculoskeletal and connective tissue disorders				
Arthralgia	2 (0.5)	5 (2.7)	3 (0.7)	10 (1.0)
Back pain	6 (1.5)	4 (2.1)	4 (1.0)	14 (1.4)
Pain in extremity	7 (1.7)	0 (0.0)	2 (0.5)	9 (0.9)

Source: Applicant's ISS, p. 47-48

A comparison with the common TEAEs reported during trials with Neurontin shows a similar pattern. No new or unexpected safety signal was discovered for G-ER based on the clinical trial safety database.

In terms of laboratory findings, the only TEAES that occurred in more than one patient (two patients each) receiving G-ER 1800mg/day were hematocrit decreased and hemoglobin decreased. There were no other laboratory abnormalities that occurred more often in the G-ER treatment groups than placebo. In addition, there was no signal related to vial sign changes in the G-ER treatment groups. There is no safety data related to electrocardiograms (ECGs), as they were performed only at screening. Refer to Dr. Jiang's review for details regarding these analyses.

The Division requested that the Applicant perform Standard MedDRA Queries (SMQs) for possible drug related serious cutaneous reactions and hepatic reactions. The results demonstrated these adverse reactions do not appear to be associated with G-ER.

The analysis of TEAEs by age, race, and gender indicated some differences in the AE profile between the individual subgroups, however no new safety signals were seen when examining TEAEs by subgroup.

Nausea (6.8% vs.1.1%) and increased weight (4.5% vs. 0.4%) occurred more frequently in the G-ER group <65 years old whereas peripheral edema (5.3% vs. 1.5%) was reported more frequently in G-ER treated subjects 65 years and over. Gastrointestinal AEs were more frequently reported in females on G-ER compared to males although no single AE term accounted for the difference. Peripheral edema occurred more frequently in females on G-ER compared to males. Over 85% of the patient population in the controlled PHN studies was Caucasian. Although the frequencies and pattern of TEAEs appear generally similar between the race categories, it is difficult to evaluate differences given the relatively small non-Caucasian population.

Open-label safety data

Open-label safety data was obtained from Study 52, an extension of study 45. Patients were treated with either G-ER 1800mg once daily or as an asymmetric BID dose for an additional 14 weeks beyond the 10 week treatment received during study 45. A total of 75/119 patients (64%) reported as least one TEAE. Infections and infestations (20.5% of all patients) and GI disorders (16.2%) were the most frequently reported SOCs for AEs. The most common AEs were upper respiratory tract infection (URTI) (6.0%), nasopharyngitis (5.1%), diarrhea, peripheral edema, and dizziness (each at 4.3%). The majority of AEs were mild or moderate in severity. There were no deaths in this study. A total of 7 SAEs were reported in 5 patients. One SAE of hypersensitivity was considered by the Investigator and Dr. Jiang to be related to study medication. Twelve patients had one or more TEAEs leading to discontinuation. Five of the AEs leading to discontinuation of study drug (abdominal pain, hypersensitivity, fatigue, myocardial infarction and gastrointestinal hemorrhage) were severe in intensity. There were no clinically significant changes in clinical laboratory parameters or vital signs measurements.

Product specific safety analysis

Because G-ER is a gastro-retentive formulation, Dr. Jiang conducted an additional safety analysis for gastrointestinal adverse events that may be related to the formulation, particularly upper GI obstruction, vomiting, and abdominal distension. The following table from Dr.

Jiang's review illustrates the results. There does not appear to be an increase in obstruction-related symptoms in the G-ER groups compared to placebo. Also, this pattern of GI TEAEs is similar to that observed during the Neurontin PHN trials.

Table 14: 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

Additionally, the Office of Surveillance and Epidemiology (OSE) performed an Adverse Event Reporting System (AERS) search for GI obstruction related postmarketing reports for two drug formulations with similar gastroretentive properties, Glumetza (metformin) and Proquin XR (ciprofloxacin). There were no reports specific to GI obstruction.

Safety Results in DPN Study 81-0046 (Study 46)

The Applicant submitted safety data for study 46, a randomized, double-blind, placebo-controlled, Phase 2 study in patients with painful diabetic peripheral neuropathy who were randomly assigned treatment with either G-ER 3000mg once daily, G-ER 3000mg asymmetric BID dose, or placebo. Patients were titrated to the randomized dose over a two week period, then received an additional 2 weeks of treatment followed by a 1 week blinded taper. A total of 70 patients received at least one dose of G-ER; 48% reported at least one TEAE. The most frequently reported TEAEs were dizziness (9.5%), somnolence (5.4%), headache (4.8%), and hypoesthesia (4.1%). The percentage of patients reporting AEs at onset by G-ER dose was greatest at the 1500, 1800 and 3000 mg/day dose level (4.8%, 4.8%, and 15.1%, respectively). The incidence of dizziness or somnolence was similar between the G-ER treatment groups regardless of dose of G-ER at onset. No patients died during the study and 1 patient (placebo group) experienced an SAE (myocardial infarction) that occurred while on treatment. Six patients (4.1%; 2 G-ER QD patients, 2 G-ER asymmetric BID patients, and 2 placebo patients) had 1 or more AE leading to discontinuation.

Postmarketing AERS Reports for Neurontin

The crude counts for all adverse events for Neurontin, as reported to the Adverse Event Reporting System (AERS), was requested of the Office of Surveillance and Epidemiology (OSE), and was conducted by Martin Pollock, Pharm.D. AERs was searched for all reports with the suspect drug name, gabapentin, from 12/30/93 (initial approval of Neurontin) to

11/19/10. This data has marked limitations, as there may be duplicate reports, and none of the reports have been reviewed to assess the possibility of relationship of the events to gabapentin.

Overall a total of 17,497 serious and nonserious reports were received from US and non US sources. The most common AEs by preferred term were drug ineffective (12%), convulsion (6%), dizziness (6%), completed suicide (6%), pain (6%), and somnolence (5%), All are labeled events.

Safety Summary for G-ER

An adequate number of patients were exposed to G-ER to satisfy the Agency's safety database requirement. The review of safety of G-ER demonstrated that G-ER at 1800mg once daily appears relatively well tolerated by patients with PHN. No new or unexpected safety signals were detected during this review, and there did not appear to be any gastrointestinal adverse events related to the gastric-retentive formulation of G-ER. The common adverse events associated with G-ER appear similar to those seen with Neurontin, and include dizziness, somnolence, headache, peripheral edema, and nausea.

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application.

10. Pediatrics

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

The Division of Scientific Investigations (DSI) conducted routine inspections of three study sites in the US that participated in Study 62. The inspections were based on the number of enrolled subjects. One site (Dr. Malhotra) was issued a voluntary action indicated (VAI) letter based on minor protocol deviations. The data generated from the three sites was determined by DSI to be adequate to support the application.

The Applicant submitted the Financial Certification and Disclosure document as required, and there appear to be no issues in this regard.

12. Labeling

The proposed proprietary name Gralise was reviewed by the Division of Medical Error Prevention and Analysis (DMEPA) was determined to be acceptable. However, if the Biopharmaceutics team requires that the established name not include "extended-release", the proprietary name may need to be re-reviewed by DMEPA.

Labeling is ongoing at the time of this writing, however an important issue that must be considered during labeling is that this medication must not be used to treat epilepsy. Neurontin is indicated for both the treatment of epilepsy and PHN. G-ER has not been studied in the treatment of epilepsy, and aspects of its pharmacokinetic profile may make it unsuitable for treatment for this condition. Drugs used for the treatment of seizures typically have a narrow therapeutic window, in contrast to analgesics which may not. Pharmaceutically, the extended-release pharmacokinetic profile of G-ER is dependent not only on its ingestion with food, but on the fat content of the food. It has also been shown to have larger fluctuations in peak and trough levels than Neurontin within any given patient. These factors may make this product unsuitable for the treatment of seizures, in that a reliable, steady serum concentration may not be obtained over time in a given patient. Additionally, G-ER has not been studied in patients with epilepsy. Therefore, this product must be labeled specifically as not to be used for the treatment of epilepsy, and not to be substituted at the pharmacy level for the treatment of epilepsy.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

G-ER 1800mg once daily has been shown to have efficacy for the treatment of postherpetic neuralgia in one adequate and well-controlled efficacy study in adults with postherpetic neuralgia. A single efficacy trial is sufficient in this setting, since the application relies in part on previous findings of safety and efficacy for Neurontin (gabapentin IR) indicated for the treatment of PHN.

Review of the submitted data did not reveal any new or unexpected safety signals associated with G-ER, and its safety profile is similar to that of Neurontin. Specifically, there did not appear to be any safety signals associated with the gastroretentive formulation, such as those related to upper GI obstruction.

Several issues arose during the Biopharmacuetics review of this application. The IVIVC model was found unacceptable, (b) (4) It was also noted that the plasma concentrations at steady state for the G-ER tablets have a higher fluctuation index (FI) when compared to Neurontin tablets.

The Clinical Review Team has conducted discussions with the Clinical Pharmacology and Biopharmacuetics review teams regarding the unacceptable IVIVC model (b) (4) (b) (4), and is in agreement with these findings. However, although pharmacokinetic data is lacking for the 300mg tablet, its use in the Phase 3 clinical trials can provide adequate support for its approval. The 300mg strength was utilized successfully in the clinical trials as part of the titration dosing to the 1800mg once daily dose of G-ER. Efficacy evaluation of the 300mg dose was not necessary, since it is planned to be used only during titration. There was

not a dedicated evaluation of the safety of the 300mg tablet, however there were not unexpected safety signals detected during the titration phases of the trials. Therefore, I recommend approval for both the 300mg and 600mg tablets.

The Biopharmaceutics team included the following comment in their review:

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.

The question to the Clinical team asks whether the higher fluctuation index for G-ER compared to Neurontin, and the variability in absorption of gabapentin based on the fat content of the meal consumed will affect the efficacy or safety of G-ER for the proposed indication. 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 fasted state. 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.

It is within the purview of the Biopharmaceutics team to determine whether the product can be granted an "extended-release" designation. Since the formulation does not meet the regulatory requirements for a product designated as such, the Applicant must propose an alternative established name that will subsequently be reviewed by the Agency.

In conclusion, the overall benefit of G-ER for the treatment of PHN outweighs the risks associated with this its use in the intended treatment population.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

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 and MedGuide are currently under review by the Office of Safety and Epidemiology/Division of Risk Management.

- Recommendation for other Postmarketing Requirements and Commitments

There are no recommended postmarketing requirements or commitments at this time.

- Recommended Comments to Applicant

None

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/s/

ELLEN W FIELDS
12/18/2010