CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 22-399/S-003

Trade Name: Horizant

Generic Name: gabapentin enacarbil

Sponsor: Xenoport Inc.

Approval Date: June 6, 2012

Indications: Management of postherpetic neuralgia (PHN) in adults.

CENTER FOR DRUG EVALUATION AND RESEARCH

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NDA 22-399/S-003

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022399/S-003

SUPPLEMENT APPROVAL

GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Eric Benson, Senior Director
Global Regulatory Affairs

Dear Mr. Benson:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 9, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Horizant (gabapentin enacarbil extended-release tablets)

We acknowledge receipt of your amendments dated September 20, October 4 and 26, November 8, 21, and 30, and December 6 and 21, 2011, and January 13 and 16, and April 25, 2012.

This "Prior Approval" supplemental new drug application proposes the addition of a new indication for the management of postherpetic neuralgia.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sharon Turner-Rinehardt, Senior Regulatory Health Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, M.D.
Deputy Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

RIGOBERTO A ROCA
06/06/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HORIZANT safely and effectively. See full prescribing information for HORIZANT.

HORIZANT (gabapentin enacarbil) Extended-Release Tablets for oral use

Initial U.S. Approval: 2011

----------RECENT MAJOR CHANGES----------

Indications and Usage, Management of Postherpetic Neuralgia (1.2)	06/2012
Dosage and Administration, Postherpetic Neuralgia (2.2)	06/2012
Dosage and Administration, Renal Impairment (2.3)	06/2012
Warnings and Precautions, Somnolence/Sedation and Dizziness (5.2)	06/2012
Warnings and Precautions, DRESS (5.5)	12/2011
Warnings and Precautions, Discontinuation of HORIZANT (5.6)	06/2012

----------INDICATIONS AND USAGE----------

HORIZANT is indicated for:

- treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults. (1.1)
- management of postherpetic neuralgia (PHN) in adults. (1.2)

---------- DOSAGE AND ADMINISTRATION ----------

Instruct patients to swallow tablets whole and not to cut, crush, or chew tablets. Take with food. (2)

RLS: 600 mg once daily taken at about 5 PM. (2.1)

- A dose of 1,200 mg once daily provided no additional benefit compared with the 600-mg dose, but caused an increase in adverse reactions. (2.1)
- If the dose is not taken at the recommended time, the next dose should be taken the following day as prescribed. (2.1)

PHN: The starting dose is 600 mg in the morning for 3 days, then increase to 600 mg twice daily beginning on day 4. (2.2)

- A daily dose greater than 1,200 mg provided no additional benefit. (2.2)
- If the dose is not taken at the recommended time, skip this dose, and the next dose should be taken at the time of next scheduled dose. (2.2)
- Patients with renal impairment: Doses of HORIZANT must be adjusted in accordance with renal function. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

Extended-Release Tablets: 300 mg and 600 mg. (3)

----------CONTRAINDICATIONS----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Driving impairment: Warn patients not to drive until they have gained sufficient experience with HORIZANT to assess whether it will impair their ability to drive. (5.1)
- Somnolence/sedation and dizziness: May impair the patient's ability to operate complex machinery. (5.2)
- HORIZANT is not interchangeable with other gabapentin products. (5.3)
- Suicidal thoughts or behaviors: HORIZANT is a prodrug of gabapentin, an antiepileptic drug (AED). AEDs increase the risk of suicidal thoughts or behaviors. Monitor for suicidal thoughts or behaviors. (5.4)

---------- ADVERSE REACTIONS ----------

- RLS: Most common adverse reactions (≥10% and at least 2 times the rate of placebo) were somnolence/sedation and dizziness. (6.1)
- PHN: Most common adverse reactions (≥10% and greater than placebo) were dizziness, somnolence, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: 06/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Restless Legs Syndrome

HORIZANT® (gabapentin enacarbil) Extended-Release Tablets are indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults.

HORIZANT is not recommended for patients who are required to sleep during the daytime and remain awake at night.

1.2 Management of Postherpetic Neuralgia

HORIZANT (gabapentin enacarbil) Extended-Release Tablets are indicated for the management of postherpetic neuralgia (PHN) in adults.

2 DOSAGE AND ADMINISTRATION

Tablets should be swallowed whole and should not be cut, crushed, or chewed.

Tablets should be taken with food.

HORIZANT is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles *[see Warnings and Precautions (5.3)]*.

2.1 Restless Legs Syndrome

The recommended dosage for HORIZANT is 600 mg once daily at about 5 PM. A daily dose of 1,200 mg provided no additional benefit compared with the 600-mg dose, but caused an increase in adverse reactions *[see Adverse Reactions (6.1)]*.

If the dose is not taken at the recommended time, the next dose should be taken the following day as prescribed.

2.2 Postherpetic Neuralgia

The recommended dosage of HORIZANT is 600 mg twice daily. HORIZANT should be initiated at a dose of 600 mg in the morning for 3 days of therapy, then increased to 600 mg twice daily (1,200 mg/day) on day four. In the 12-week principal efficacy study, additional benefit of using doses greater than 1,200 mg a day was not demonstrated, and these higher doses resulted in an increase in adverse reactions *[see Adverse Reactions (6.1)]*.

If the dose is not taken at the recommended time, skip this dose, and the next dose should be taken at the time of the next scheduled dose.

2.3 Renal Impairment

Dosing of HORIZANT is adjusted in accordance with renal function, as represented by creatinine clearance *[see Clinical Pharmacology (12.3)]*. Target dose regimens are listed in Table 1 and Table 2.

Table 1. Dosage of HORIZANT for Patients With Restless Legs Syndrome in Accordance With Creatinine Clearance

Creatinine Clearance (mL/min)	Target Dose Regimen
≥60	600 mg per day
30 - 59	Start at 300 mg per day and increase to 600 mg as needed
15 - 29	300 mg per day
<15	300 mg every other day
<15 on hemodialysis	Not recommended

Table 2. Dosage of HORIZANT for Patients With Postherpetic Neuralgia in Accordance With Creatinine Clearance

Creatinine Clearance (mL/min)	Titration	Maintenance	Tapering
≥60	600 mg in AM for 3 days	600 mg twice daily	600 mg in AM for 1 week
30 - 59	300 mg in AM for 3 days	300 mg twice daily. Increase to 600 mg twice daily as needed[a]	Reduce current maintenance dose to once daily in AM for 1 week
15 - 29	300 mg in AM on Day 1 and Day 3	300 mg in AM. Increase to 300 mg twice daily if needed[a]	If taking 300 mg twice daily, reduce to 300 mg once daily in AM for 1 week. If taking 300 mg once daily, no taper needed.
<15	None	300 mg every other day in AM. Increase to 300 mg once daily in AM if needed[a]	None
<15 on hemodialysis	None	300 mg following every dialysis. Increase to 600 mg following every dialysis if needed[a]	None

[a] Based on tolerability and efficacy

In patients with stable renal function, CrCl can be estimated using the equation of Cockcroft and Gault:

for males: CrCl = (140-age)(weight)/[(72)(SCr)]

for females: CrCl = (0.85)(140-age)(weight)/[(72)(SCr)]

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

3 DOSAGE FORMS AND STRENGTHS

HORIZANT Extended-Release Tablets, 300 mg, are red, oval-shaped tablets debossed with "GS TF7" and 600 mg, are white to off-white, oval-shaped tablets debossed with "GS LFG". Both the 300 mg and 600 mg tablets may contain occasional black/grey spots.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Effects on Driving

HORIZANT causes significant driving impairment. Patients being treated with HORIZANT should not drive until they have gained sufficient experience to assess whether HORIZANT impairs their ability to drive. However, prescribers and patients should be aware that patients' ability to assess their own driving competence, as well as their ability to assess the degree of somnolence caused by HORIZANT, can be imperfect.

In a 2-week simulated driving study in patients with RLS, a daily single 1,200-mg dose of HORIZANT caused significant impairment within 2 hours and for up to 14 hours after dosing. The impairment was similar to that caused by the active control, a single oral dose of diphenhydramine 50 mg. The effect on driving at times other than 2 weeks is unknown. Whether the impairment is related to somnolence *[see Warnings and Precautions (5.2)]* or other effects of HORIZANT is unknown. The 600-mg dose was not studied. Because a 600-mg/day dose of HORIZANT can cause significant somnolence, similar to that of the 1,200-mg/day dose *[see Warnings and Precautions (5.2)]*, the 600- and 1,200-mg/day doses may have similar effects on driving behavior.

5.2 Somnolence/Sedation and Dizziness

HORIZANT causes somnolence/sedation and dizziness (see Tables 4 and 5). Patients should be advised not to drive a car or operate other complex machinery until they have gained sufficient experience on HORIZANT to assess whether HORIZANT impairs their ability to perform these tasks.

During the controlled trials in patients with RLS, somnolence/sedation was reported in 20% of patients treated with 600 mg of HORIZANT per day compared with 6% of patients receiving placebo. In those patients treated with HORIZANT who reported somnolence, the somnolence persisted during treatment in about 30%. In the remaining patients, symptoms resolved within 3 to 4 weeks. Dizziness was reported in 13% of patients receiving 600 mg of HORIZANT per day compared with 4% of patients receiving placebo. In those patients treated with HORIZANT who reported dizziness, symptoms persisted during treatment in about 20%. Somnolence/sedation led to withdrawal in 2% of patients receiving 600 mg of HORIZANT per day. Dizziness led to withdrawal in 1% of patients receiving 600 mg of HORIZANT per day. The incidence of these adverse reactions was greater in the patients receiving 1,200 mg per day.

During the 12-week, controlled study in patients with PHN, somnolence was reported in 10% of patients treated with 1,200 mg of HORIZANT per day compared with 8% of patients receiving placebo. Fatigue/asthenia was reported in 6% of patients treated with 1,200 mg of HORIZANT per day compared with 1% of patients receiving placebo. In those patients treated with 1,200 mg of HORIZANT per day who reported somnolence (10%), the somnolence persisted during treatment in about 27%. In the remaining patients, symptoms resolved within 4 to 5 weeks. Dizziness was reported in 17% of patients receiving 1,200 mg of HORIZANT per day compared with 15% of patients receiving placebo. In those patients treated with 1,200 mg of HORIZANT per day who reported dizziness, symptoms persisted during treatment in about 6%. Somnolence led to withdrawal in <1% of patients receiving 1,200 mg of HORIZANT per day compared with 2% of patients receiving placebo. Dizziness led to withdrawal in 2% of patients receiving 1,200 mg of HORIZANT per day compared with 3% of patients receiving placebo.

5.3 Lack of Interchangeability With Gabapentin

HORIZANT is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles. The same dose of HORIZANT results in different plasma concentrations of gabapentin relative to other gabapentin products. *[See Clinical Pharmacology (12.3).]*

The safety and effectiveness of HORIZANT in patients with epilepsy have not been studied.

5.4 Suicidal Behavior and Ideation

HORIZANT (gabapentin enacarbil) is a prodrug of gabapentin, an antiepileptic drug (AED). AEDs increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Because HORIZANT is a prodrug of gabapentin, HORIZANT also increases this risk. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (monotherapy and adjunctive therapy) of 11 different AEDs showed that patients randomized to 1 of the AEDs had approximately twice the risk [adjusted relative risk 1.8, 95% confidence interval (CI): 1.2, 2.7] of suicidal thinking or behavior compared with patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared with 0.24% among 16,029 placebo-treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 3. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients With Events Per 1,000 Patients	Drug Patients With Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients With Events Per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing HORIZANT must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that HORIZANT increases the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.5 Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including gabapentin. HORIZANT is a prodrug of gabapentin. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute

viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved.

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. HORIZANT should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

5.6 Discontinuation of HORIZANT

When discontinuing HORIZANT, patients with RLS receiving 600 mg or less once daily can discontinue the drug without tapering. If the recommended dose is exceeded, the dose should be reduced to 600 mg daily for 1 week prior to discontinuation to minimize the potential of withdrawal seizure.

In patients with PHN receiving HORIZANT twice daily, the dose should be reduced to once daily for 1 week prior to discontinuation to minimize the potential of withdrawal seizure, see Table 2 *[see Dosage and Administration (2.3)]*.

5.7 Tumorigenic Potential

In an oral carcinogenicity study, gabapentin enacarbil increased the incidence of pancreatic acinar cell adenoma and carcinoma in male and female rats *[see Nonclinical Toxicology (13.1)]*. The clinical significance of this finding is unknown.

In clinical studies of gabapentin as adjunctive therapy in epilepsy comprising 2,085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of gabapentin. Without knowledge of the background incidence and recurrence in a similar population not treated with gabapentin, it is impossible to know whether the incidence reported in this cohort is or is not affected by treatment.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in the *Warnings and Precautions* section of the label:

- Somnolence/sedation and dizziness *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In all controlled and uncontrolled trials across various patient populations, more than 2,300 patients have received HORIZANT orally in daily doses ranging from 600 to 3,600 mg.

Restless Legs Syndrome: The exposure to HORIZANT in 1,201 patients with RLS included 613 exposed for at least 6 months and 371 exposed for at least 1 year. HORIZANT in the treatment of RLS was studied primarily in placebo-controlled trials (n = 642), and in long-

term follow-up studies. The population with RLS ranged from 18 to 82 years of age, with 60% being female and 95% being Caucasian.

The safety of HORIZANT in doses ranging from 600 to 2,400 mg has been evaluated in 515 patients with RLS in 3 double-blind, placebo-controlled, 12-week clinical trials. The 600-mg dose was studied in 2 of the 3 studies. Eleven out of 163 (7%) patients treated with 600 mg of HORIZANT discontinued treatment due to adverse reactions compared with 10 of the 245 (4%) patients who received placebo.

The most commonly observed adverse reactions (≥5% and at least 2 times the rate of placebo) in these trials for the 600-mg dose of HORIZANT were somnolence/sedation and dizziness (see Table 4). Table 4 lists treatment-emergent adverse reactions that occurred in ≥2% of patients with RLS treated with HORIZANT and numerically greater than placebo.

Table 4. Incidence of Adverse Reactions in 12-Week RLS Studies Reported in ≥2% of Patients Treated With 600 or 1,200 mg of HORIZANT and Numerically Greater Than Placebo

Body System/Adverse Reaction	Placebo[a] (N = 245) %	HORIZANT 600 mg/day[b] (N = 163) %	HORIZANT 1,200 mg/day[c] (N = 269) %
Nervous system disorders			
Somnolence/sedation	6	20	27
Dizziness	4	13	22
Headache	11	12	15
Gastrointestinal disorders			
Nausea	5	6	7
Dry mouth	2	3	4
Flatulence	<1	3	2
General disorders and administration site conditions			
Fatigue	4	6	7
Irritability	1	4	4
Feeling drunk	0	1	3
Feeling abnormal	<1	<1	3
Peripheral edema	1	<1	3
Metabolism and nutritional disorders			
Weight increased	2	2	3
Increased appetite	<1	2	2
Ear and labyrinth disorders			
Vertigo	0	1	3
Psychiatric disorders			
Depression	<1	<1	3
Libido decreased	<1	<1	2

[a] Placebo was a treatment arm in each of the 3 double-blind, placebo-controlled, 12-week clinical trials.

[b] The 600-mg dose of HORIZANT was a treatment arm in 2 of the 3 double-blind, placebo-controlled, 12-week clinical trials.

[c] The 1,200-mg dose of HORIZANT was a treatment arm in each of the 3 double-blind, placebo-controlled, 12-week clinical trials.

Adverse reactions reported in these three 12-week studies in <2% of patients treated with 600 mg of HORIZANT and numerically greater than placebo were balance disorder, blurred vision, disorientation, feeling drunk, lethargy, and vertigo.

The following adverse reactions were dose-related: somnolence/sedation, dizziness, feeling drunk, libido decreased, depression, headache, peripheral edema, and vertigo.

Postherpetic Neuralgia: The exposure to HORIZANT in 417 patients with PHN included 207 patients exposed for at least 3 months. Overall, the mean age of patients in the PHN studies ranged from 61 to 64 years of age across dose groups; the majority of patients were male (45% to 61%) and Caucasian (80% to 98%).

The safety of HORIZANT in doses ranging from 1,200 to 3,600 mg has been evaluated in 417 patients with PHN in 3 clinical studies. The principal efficacy study evaluating the efficacy and safety of HORIZANT in the management of PHN was a 12-week, double-blind, multicenter study comparing 1,200 mg/day, 2,400 mg/day and 3,600 mg/day to placebo. Six out of 107 (6%) patients treated with 1,200 mg of HORIZANT discontinued treatment due to adverse events compared with 12 of the 95 (13%) patients who received placebo.

The most commonly observed adverse reactions (≥10% and greater than placebo) in this trial for the 1,200 mg dose of HORIZANT were dizziness, somnolence and headache (see Table 5). Table 5 lists treatment-emergent adverse reactions that occurred in ≥2% of patients with PHN treated with HORIZANT 1,200 mg/day and numerically greater than placebo.

Table 5. Incidence of Adverse Reactions (in At Least 2% of Patients Treated With 1,200 mg/day of HORIZANT and Numerically Greater Than the Placebo Rate) Reported in All Patients in the 12-Week PHN Study

	Percent of patients			
Body System/Adverse Reaction	Placebo (N = 95)	HORIZANT 1,200 mg/day (N = 107)	HORIZANT 2,400 mg/day (N = 82)	HORIZANT 3,600 mg/day (N = 87)
Nervous System				
Dizziness	15	17	26	30
Somnolence	8	10	11	14
Headache	9	10	10	7
Gastrointestinal disorders				
Nausea	5	8	4	9
General disorders and administration site conditions				
Fatigue/Asthenia	1	6	4	10
Peripheral edema	0	6	7	6
Psychiatric disorders				
Insomnia	2	3	5	7
Metabolism and nutritional disorders				
Weight increased	1	3	5	5
Eye disorders				
Blurred vision	0	2	5	2

The following adverse reactions were also reported as ≥2% at 2,400 mg/day and/or 3,600 mg/day and appeared to be dose-related but were <2% at 1,200 mg/day: balance disorder,

confusional state, depression, dry mouth, flatulence, increased appetite, irritability, and vertigo. Dizziness, somnolence, fatigue, and insomnia appeared to show a dose relationship.

6.2 Adverse Events Associated With Gabapentin

The following adverse events have been reported in patients receiving gabapentin, either in clinical trials or postmarketing: breast enlargement and gynecomastia.

7 DRUG INTERACTIONS

Neither gabapentin enacarbil nor gabapentin are substrates, inhibitors, or inducers of the major cytochrome P450 enzymes. Gabapentin enacarbil is neither a substrate nor an inhibitor of P-glycoprotein *in vitro [See Clinical Pharmacology (12.3)]*.

Pharmacokinetic drug-drug interaction studies were conducted to examine the potential for an interaction of gabapentin enacarbil with cimetidine and naproxen. No significant pharmacokinetic interactions were observed. No clinically relevant pharmacokinetic interactions are expected between HORIZANT and other substrates of organic cation transporter type 2 (OCT2) and monocarboxylate transporter type 1 (MCT-1) *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies with HORIZANT in pregnant women. In nonclinical studies in rat and rabbits, administration of gabapentin enacarbil was developmentally toxic when administered to pregnant animals at doses and gabapentin exposures greater than those used clinically. HORIZANT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When pregnant rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or 5,000 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was increased at the 2 highest doses and fetal body weights were decreased at the high dose. The no-effect dose for embryo-fetal developmental toxicity in rats (200 mg/kg/day) represents approximately 2 times the gabapentin exposure associated with the maximum recommended human dose (MRHD) of 1,200 mg/day gabapentin enacarbil on an area under the curve (AUC) basis.

When pregnant rabbits were administered gabapentin enacarbil (oral doses of 200, 500, or 2,500 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was increased and fetal body weights were decreased at the high dose. The no-effect dose for embryo-fetal developmental toxicity in rabbits (500 mg/kg/day) represents approximately 9 times the gabapentin exposure associated with the MRHD of 1,200 mg/day gabapentin enacarbil on an AUC basis.

When female rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or 5,000 mg/kg/day) throughout the pregnancy and lactation periods, offspring growth and survival were decreased at the two highest doses. The no-effect dose for pre- and post-natal developmental toxicity in rats is approximately 2 times the MRHD on an AUC basis.

In reproductive and developmental studies of gabapentin, developmental toxicity was observed at all doses tested. Increased incidences of hydroureter and/or hydronephrosis were

observed in rat offspring following treatment of pregnant animals in studies of fertility and general reproductive performance, embryo-fetal development, and peri- and post-natal development. Overall, a no-effect dose was not established. In mice, treatment of pregnant animals with gabapentin during the period of organogenesis resulted in delayed fetal skeletal ossification at all but the lowest dose tested. When pregnant rabbits were treated with gabapentin during the period of organogenesis, an increase in embryo-fetal mortality was observed at all doses of gabapentin tested.

In a published study, gabapentin (400 mg/kg/day) was administered by intraperitoneal injection to neonatal mice during the first postnatal week, a period of synaptogenesis in rodents (corresponding to the last trimester of pregnancy in humans). Gabapentin caused a marked decrease in neuronal synapse formation in brains of intact mice and abnormal neuronal synapse formation in a mouse model of synaptic repair. Gabapentin has been shown *in vitro* to interfere with activity of the $\alpha 2\delta$ subunit of voltage-activated calcium channels, a receptor involved in neuronal synaptogenesis. The clinical significance of these findings is unknown.

8.2 Labor and Delivery

The effect of HORIZANT on labor and delivery is unknown.

8.3 Nursing Mothers

It is not known whether gabapentin derived from HORIZANT is secreted in human milk; however, gabapentin is secreted into human milk following oral administration of gabapentin products. Because of the potential for adverse reactions in nursing infants from HORIZANT, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of HORIZANT in pediatric patients have not been studied.

8.5 Geriatric Use

Of the 515 patients treated with HORIZANT in the 3 double-blind, placebo-controlled, 12-week clinical trials for RLS, 11% were 65 to 74 years of age and 1% were 75 years of age and older. Clinical trials of HORIZANT for the treatment of RLS did not include a sufficient number of patients 65 years and older to determine whether they respond differently from younger individuals.

In the 12-week, double-blind, placebo-controlled study of HORIZANT for the management of PHN (n=276 patients treated with HORIZANT), 37% were 65 to 74 years of age and 13% were 75 years of age and older. The overall incidence of adverse events was comparable between the patients aged ≥18 to <65 years and ≥65 to <74 years. No overall differences in the safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Gabapentin is known to be almost exclusively excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because

elderly patients are more likely to have decreased renal function, the frequency of dosing may need to be adjusted based on calculated creatinine clearance in these patients *[see Dosage and Administration (2.3)]*.

8.6 Renal Impairment

The dose of HORIZANT should be adjusted in patients with renal impairment *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

HORIZANT, a prodrug of gabapentin, is not a scheduled drug.

9.2 Abuse

Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta or kappa), or cannabinoid 1 receptor sites. A small number of postmarketing cases report gabapentin misuse and abuse. These individuals were taking higher than recommended doses of gabapentin for unapproved uses. Most of the individuals described in these reports had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances.

When prescribing products that deliver gabapentin, carefully evaluate patients for a history of drug abuse and observe them for signs and symptoms of gabapentin misuse or abuse (e.g., development of tolerance, self dose escalation, and drug-seeking behavior).

9.3 Dependence

There are rare postmarketing reports of individuals experiencing withdrawal symptoms shortly after discontinuing higher than recommended doses of gabapentin used to treat illnesses for which the drug is not approved. Such symptoms included agitation, disorientation, and confusion after suddenly discontinuing gabapentin that resolved after restarting gabapentin. Most of these individuals had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances. The dependence and abuse potential of gabapentin has not been evaluated in human studies.

10 OVERDOSAGE

10.1 Human Overdose Experience

There have been no reports describing individuals who have taken an overdose of HORIZANT. The highest single dose of gabapentin enacarbil administered to date is 6,000 mg in healthy subjects. At this supratherapeutic dose there were no serious adverse events. The incidence of central nervous system adverse reactions, particularly dizziness and somnolence/sedation, is increased with doses greater than 600 mg daily.

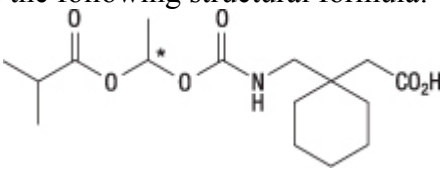
10.2 Overdosage Management

In the event of an overdose, the patient should be treated supportively with appropriate monitoring as necessary. Gabapentin derived from gabapentin enacarbil can be removed from plasma by hemodialysis. The mean percentage of gabapentin recovered following hemodialysis in patients with end-stage renal disease was 29% (expressed as a proportion of the gabapentin released from HORIZANT).

Further management should be as clinically indicated or as recommended by a poison control center.

11 DESCRIPTION

HORIZANT (gabapentin enacarbil) is a prodrug of gabapentin. Gabapentin enacarbil is described as (1-{[({(1*RS*)-1-[(2-Methylpropanoyl)oxy]ethoxy}carbonyl)amino]methyl} cyclohexyl) acetic acid. It has a molecular formula of $C_{16}H_{27}NO_6$ and a molecular weight of 329.39. It is a racemate and has the following structural formula:



Gabapentin enacarbil is a white to off-white crystalline solid with a melting onset of approximately 64°C and a solubility of 0.5 mg/mL in water and 10.2 mg/mL in phosphate buffer (pH 6.3).

HORIZANT is administered orally. Each HORIZANT Extended-Release Tablet contains 300 mg or 600 mg of gabapentin enacarbil and the following inactive ingredients: colloidal silicon dioxide, dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium stearate, sodium lauryl sulfate, and talc. The 300 mg tablets also contain red ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gabapentin enacarbil is a prodrug of gabapentin and, accordingly, its therapeutic effects in RLS and PHN are attributable to gabapentin.

The precise mechanism by which gabapentin is efficacious in RLS and PHN is unknown.

The mechanism of action by which gabapentin is efficacious in PHN is unknown but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test), but does not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to human pain is not known.

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. Gabapentin enacarbil and gabapentin have been tested in radioligand binding assays, and neither exhibited affinity for a number of other common receptor, ion channel, or transporter proteins.

In vitro studies have shown that gabapentin binds with high affinity to the α2δ subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of gabapentin enacarbil in RLS and PHN is unknown.

12.3 Pharmacokinetics

HORIZANT is an extended-release formulation of gabapentin enacarbil, a prodrug of gabapentin. HORIZANT provides approximately dose-proportional and extended exposure to gabapentin over the range 300 to 6,000 mg. HORIZANT and gabapentin are not interchangeable because the same daily dose of each results in different plasma concentrations of gabapentin.

For subjects with PHN taking HORIZANT 600 mg twice daily, the estimated steady state mean C_{max} was 5.35 μg/mL, mean AUC_{24} was approximately 109 μg*hr/mL, mean C_{min} was 3.63 μg/mL, and mean peak trough ratio was 1.5.

Absorption: The pathway for absorption of gabapentin enacarbil is believed to include active transport via a proton-linked monocarboxylate transporter, MCT-1. This transporter is expressed at high levels in the intestinal tract and is not saturated by administration of high doses of HORIZANT. Mean bioavailability of gabapentin (based on urinary recovery of gabapentin) for HORIZANT in the fed state is about 75%. Bioavailability under fasting conditions has been estimated by gabapentin urinary recovery to be 42% to 65%. In a food effect study, the exposure of gabapentin increased by 24%, 34%, and 44% with low, moderate, and high fat meals, respectively. The T_{max} of gabapentin after administration of 600 mg of HORIZANT was 5.0 hours in fasted subjects and 7.3 hours in fed subjects. Steady state is reached in 2 days with daily administration.

Distribution: Plasma protein binding of gabapentin has been reported to be <3%. The apparent volume of distribution of gabapentin in subjects receiving HORIZANT is 76 L.

Metabolism: After oral administration, gabapentin enacarbil undergoes extensive first-pass hydrolysis by non-specific carboxylesterases primarily in enterocytes and to a lesser extent in the liver, to form gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid. Levels of gabapentin enacarbil in blood are low and transient (≤2% of corresponding gabapentin plasma levels). Released gabapentin is not appreciably metabolized in humans. Neither gabapentin enacarbil nor gabapentin are substrates, inhibitors, or inducers of the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). Gabapentin enacarbil is neither a substrate nor an inhibitor of P-glycoprotein *in vitro*.

Elimination: Following hydrolysis of gabapentin enacarbil, the released gabapentin is excreted unchanged by the kidney. Gabapentin renal excretion is believed to involve a component of active secretion via an organic cation transporter (OCT2) present in the kidney. In a human pharmacokinetic study with immediate release ^{14}C gabapentin enacarbil, mean recovery of total radioactivity in urine was 94%, with 5% of the radioactive dose recovered in feces.

Apparent oral clearance (CL/F) of gabapentin from plasma after dosing of HORIZANT with food ranged from 6.0 to 9.3 L/hr. Following oral dosing of HORIZANT, plasma clearance of gabapentin is approximately proportional to creatinine clearance. Renal clearance (CLr) of gabapentin ranged from 5 to 7 L/hr, regardless of food intake or food type. The elimination half-life ($t_{½}$) of gabapentin ranges from 5.1 to 6.0 hours and is unaltered by dose or following multiple doses of HORIZANT.

Special Populations: *Race:* In the population pharmacokinetic study, the majority (94%) of subjects in the clinical studies was Caucasian, and no single other race was greater than 4%; therefore, the effect of race could not be studied.

Gender: There are no clinically meaningful differences in pharmacokinetics of HORIZANT between male and female patients.

Geriatric Patients: There are no clinically significant differences in pharmacokinetics of HORIZANT between geriatric patients (≥65 years of age) and younger patients (18 to <65 years of age). However, the pharmacokinetics in geriatric patients may be affected by an age-related decline in renal function *[see Use in Specific Populations (8.5)]*.

Renal Impairment: Gabapentin clearance after dosing with HORIZANT is approximately proportional to CrCl. Apparent oral clearance (CL/F) decreased in moderate (4.2 L/hr) and severe renal impairment patients (1.7 L/hr) compared with 6.0 to 9.3 L/hr in patients without renal impairment. Similarly, CLr was decreased to 3 and 1 L/hr in moderate and severe renal impairment patients, respectively, compared with 5 to 7 L/hr in non-renal impairment patients. Dosage reduction in patients with renal dysfunction not on dialysis is necessary.

Gabapentin is effectively removed from plasma by hemodialysis. The mean percentage of gabapentin recovered following hemodialysis in patients with end-stage renal disease was 29% (expressed as a proportion of the gabapentin released from HORIZANT). For patients with PHN on hemodialysis, dosage reduction is required *[see Dosage and Administration (2.3)]*. For patients with RLS on hemodialysis, treatment with HORIZANT is not recommended *[see Dosage and Administration (2.3)]*.

Drug Interactions: *Cimetidine:* Gabapentin released from HORIZANT is eliminated by renal clearance via OCT2. Cimetidine is a known substrate for this same elimination pathway. Coadministration of 1,200 mg of HORIZANT once daily with cimetidine 400 mg 4 times daily showed no effect on cimetidine exposure. There was an increase in AUC of gabapentin (24%) and a decrease in renal clearance of gabapentin (20%); these effects are not expected to be clinically relevant. No clinically relevant pharmacokinetic interactions are expected between HORIZANT and other substrates of OCT2.

Naproxen: The pathway for absorption of gabapentin enacarbil includes active transport via a proton-linked MCT-1. Coadministration of 1,200 mg of HORIZANT once daily with naproxen 500 mg twice daily, a known substrate of MCT-1, showed no effect on naproxen exposure or steady-state gabapentin C_{max} and AUC. No clinically relevant pharmacokinetic interactions are expected between HORIZANT and other substrates of MCT-1.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Oral (gavage) carcinogenicity studies were conducted in mice and rats. In mice, gabapentin enacarbil was tested at doses of 500, 2,000, or 5,000 mg/kg/day for up to

104 weeks. There was no evidence of drug-related carcinogenicity. The highest dose tested is 16 times the MRHD of 1,200 mg/day, on a plasma AUC basis.

In rats, gabapentin enacarbil was tested at doses of 500, 2,000, or 5,000 mg/kg/day for up to 97 weeks in mid-dose males, 90 weeks in high-dose males, and 104 weeks in females. The plasma exposures (AUC) for gabapentin at these doses are approximately 4, 17, and 37 times, respectively, that in humans at the MRHD. Increases in the incidence of pancreatic acinar adenoma and carcinoma were found in mid-dose males and high-dose males and females.

In 2-year dietary carcinogenicity studies of gabapentin, no evidence of drug-related carcinogenicity was observed in mice treated at doses up to 2,000 mg/kg/day. In rats, increases in the incidence of pancreatic acinar cell adenoma and carcinoma were found in male rats receiving the highest dose (2,000 mg/kg), but not at doses of 250 or 1,000 mg/kg/day. At 1,000 mg/kg/day, the plasma AUC for gabapentin is estimated to be approximately 13 times that in humans at the MRHD.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and thus may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including human.

Mutagenesis: Gabapentin enacarbil was negative in *in vitro* bacterial reverse mutation (Ames) and *in vivo* rat micronucleus assays. In an *in vitro* human lymphocyte assay, there was an increase in the number of chromosomal aberrations with gabapentin enacarbil. This *in vitro* response was attributed to acetaldehyde released by hydrolysis of gabapentin enacarbil during the incubation period. Acetaldehyde is known to cause chromosome aberrations *in vitro*, but is readily metabolized *in vivo*. The small quantity of acetaldehyde formed from gabapentin enacarbil *in vivo* is rapidly cleared by normal metabolic activity.

Impairment of Fertility: Oral administration of gabapentin enacarbil (doses of 0, 200, 1,000, or 5,000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females up to day 7 of gestation resulted in no adverse effects on fertility. The highest dose tested is approximately 39 times the MRHD on an AUC basis.

14 CLINICAL STUDIES

14.1 Restless Legs Syndrome (RLS) 12-Week Pivotal Studies

The effectiveness of HORIZANT in the treatment of moderate-to-severe primary RLS was demonstrated in two 12-week clinical studies in adults diagnosed with RLS using the International Restless Legs Syndrome Study Group diagnostic criteria. Key diagnostic criteria for RLS are: an urge to move the legs usually accompanied or caused by uncomfortable and unpleasant leg sensations, symptoms begin or worsen during periods of rest or inactivity such as lying or sitting, symptoms are partially or totally relieved by movement such as walking or stretching at least as long as the activity continues, and symptoms are worse or occur only in the evening or night. Patients were required to have a total score of ≥15 on the International Restless

Legs Syndrome (IRLS) Rating Scale at baseline. Patients with RLS secondary to other conditions (e.g., pregnancy, renal failure, iron deficiency anemia) were excluded. In study 1, patients were randomized to receive 1,200 mg of HORIZANT (N = 112) or placebo (N = 108) taken once daily at about 5 PM with food. In study 2, patients were randomized to receive 600 mg of HORIZANT (N = 114), 1,200 mg of HORIZANT (N = 111), or placebo (N = 96) taken once daily at about 5 PM with food.

Efficacy was evaluated using the IRLS Rating Scale and Clinical Global Impression of Improvement (CGI-I) scores. The IRLS Rating Scale contains 10 items designed to assess the severity of sensory and motor symptoms, sleep disturbance, daytime somnolence/sedation, and impact on activities of daily living and mood associated with RLS. The range of scores is 0 to 40, with 0 being absence of RLS symptoms and 40 the most severe symptoms. The CGI-I Scale allows the investigator to rate the patient's overall change in RLS symptoms since baseline, whether or not in the opinion of the investigator the change is related to study drug treatment. The change from baseline in the IRLS Rating Scale at Week 12 and the proportion of responders on the CGI-I Scale defined as a rating of "much improved" or "very much improved" at Week 12 were co-primary outcomes in these studies.

In these 2 studies, the mean age of patients studied was 50 years (range: 18 to 81 years); 59% of the patients were female. The racial distribution for these studies was as follows: Caucasian, 95%; black, 2%; and other, 3%.

Statistically significant differences ($P<0.05$) between the treatment groups receiving 600 and 1,200 mg of HORIZANT and the group receiving placebo were observed at Week 12 for both the mean change from baseline in the IRLS Scale total score and the proportion of responders ("much improved" or "very much improved") on the CGI-I Scale as described in Table 6.

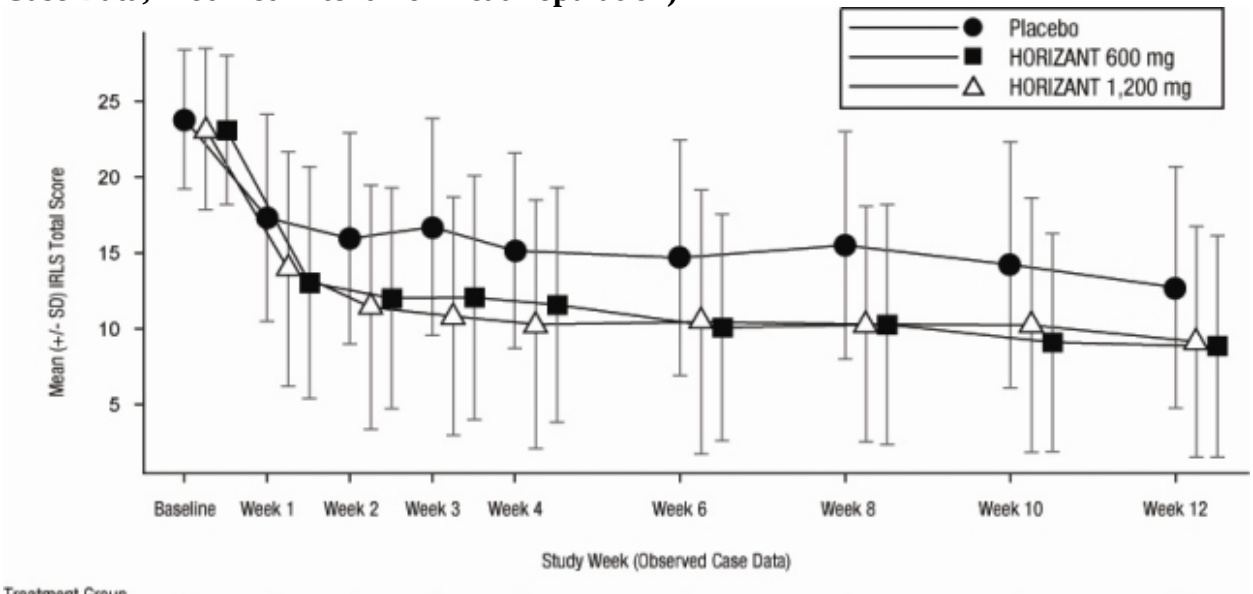
Table 6. Mean Change in IRLS Scale Total Score and Proportion of Responders on CGI-I Scale at Week 12

	Study 1		Study 2		
Week 12	HORIZANT 1,200 mg (N = 112)	Placebo (N = 108)	HORIZANT 600 mg (N = 114)	HORIZANT 1,200 mg (N = 111)	Placebo (N = 96)
Mean Change in IRLS Score	-13.2	-8.8	-13.8	-13.0	-9.8
Proportion of Responders[a] on CGI-I	76%	39%	73%	77%	45%

[a] CGI-I Responders = "much improved" and "very much improved."

Figure 1 presents the improvement in mean IRLS Rating Scale total score in patients treated with placebo or 600 or 1,200 mg of HORIZANT over the 12 weeks of treatment in study 2.

Figure 1. Study 2, Mean (±SD) IRLS Rating Scale Total Score Over 12 Weeks (Observed Case Data, Modified Intent-To-Treat Population)



Treatment Group	n	n	n	n	n	n	n	n	n
Placebo	96	88	91	87	84	83	81	74	74
HORIZANT 600 mg	114	110	110	105	104	102	102	103	101
HORIZANT 1,200 mg	111	104	102	103	101	97	95	97	93

14.2 Postherpetic Neuralgia (PHN) 12-Week Study

The efficacy of HORIZANT for the management of postherpetic neuralgia was established in a multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-week study evaluating the efficacy, safety, and dose response of 3 maintenance doses of HORIZANT (1,200, 2,400, and 3,600 mg/day, with 107, 82, and 87 patients in each dosing group, respectively). Patients greater than 18 years of age with a documented medical diagnosis of PHN of at least three months duration were enrolled. To ensure that patients had significant pain, randomized patients were required to have a minimum baseline 24-hour average Pain Intensity Numerical Rating Scale (PI-NRS) intensity score of at least 4.0 on the 11-point numerical PI-NRS, ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine").

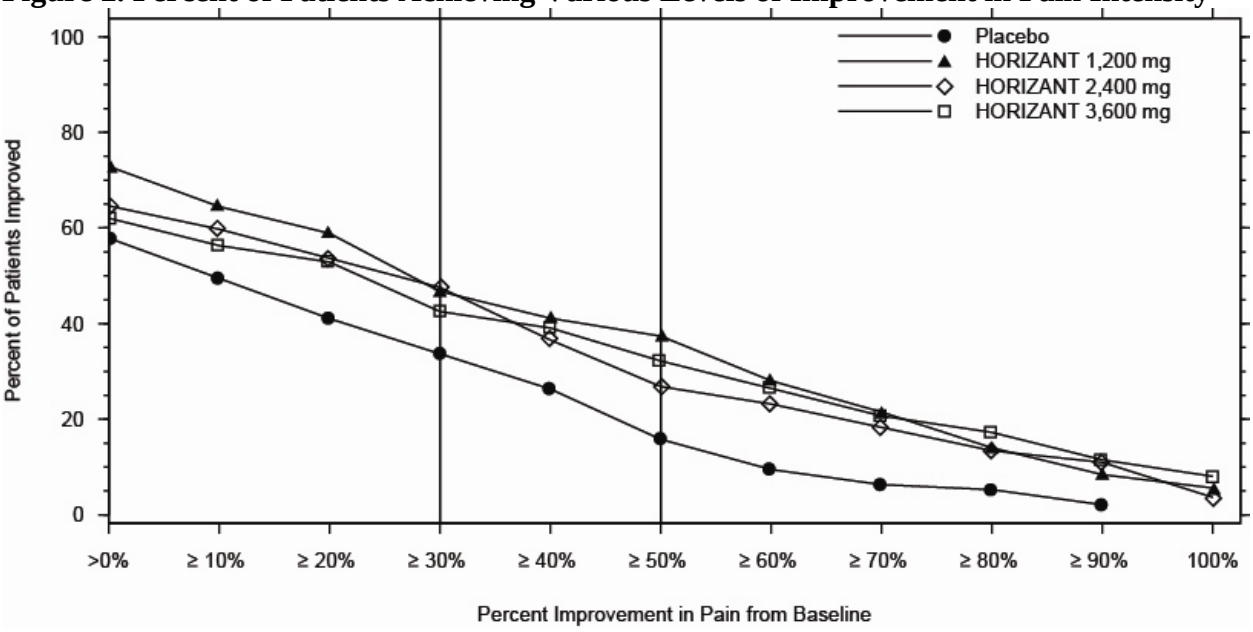
In this study, a total of 276 patients received HORIZANT while 95 patients received placebo. Following a 1-week baseline period during which patients were screened for eligibility, patients began a 1-week up-titration period followed by a 12-week maintenance treatment period, and then a 1-week down-titration period.

Treatment with HORIZANT statistically significantly improved the mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline at all doses tested. A benefit over placebo was observed for all 3 doses of HORIZANT as early as Week 1 and maintained to the end of treatment. Additional benefit of using doses of greater than 1,200 mg a day was not demonstrated.

For various degrees of improvement in pain from baseline to end of maintenance treatment, Figure 2 shows the fraction of patients achieving that degree of improvement. The

figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement.

Figure 2. Percent of Patients Achieving Various Levels of Improvement in Pain Intensity



16 HOW SUPPLIED/STORAGE AND HANDLING

HORIZANT Extended-Release Tablets containing 300 mg of gabapentin enacarbil are red, with occasional black/grey spots, oval-shaped tablets debossed with "GS TF7".

HORIZANT Extended-Release Tablets containing 600 mg of gabapentin enacarbil are white to off-white, with occasional black/grey spots, oval-shaped tablets debossed with "GS LFG". They are supplied as follows:

300 mg: NDC 0173-0832-13: Bottles of 30

600 mg: NDC 0173-0806-01: Bottles of 30

Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Do not remove desiccants. Dispense in original bottle.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Physicians should instruct their patients to read the Medication Guide before starting therapy with HORIZANT and to reread it upon prescription renewal for new information regarding the use of HORIZANT.

17.1 Effects on Driving

Patients should be told that HORIZANT can cause significant driving impairment. Accordingly, they should be advised not to drive a car until they have gained sufficient experience on HORIZANT to assess whether HORIZANT impairs their ability to drive. Patients should be told that it is not known how long this effect lasts.

17.2 Somnolence/Sedation and Dizziness

Patients should be told that HORIZANT can cause significant somnolence and dizziness. This typically resolves within several weeks of initiating treatment. Accordingly, they should be told not to operate dangerous machinery until they have gained sufficient experience on HORIZANT to assess whether HORIZANT impairs their ability to operate dangerous machinery safely.

17.3 Suicidal Behavior and Ideation

Patients, their caregivers, and families should be counseled that HORIZANT may increase the risk of suicidal thoughts and behavior, and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

17.4 Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Patients should be instructed that multiorgan hypersensitivity reactions may occur with HORIZANT. Patients should contact their physician immediately if they experience any signs or symptoms of these conditions *[see Warnings and Precautions (5.5)]*.

17.5 Lack of Interchangeability With Gabapentin

Patients should be advised that doses of HORIZANT and other gabapentin products are not interchangeable.

17.6 Dosing Instructions

- Patients should be instructed to take HORIZANT only as prescribed.
- Tablets should be swallowed whole and should not be cut, crushed, or chewed.
- Tablets should be taken with food.
- For Restless Legs Syndrome, 600 mg HORIZANT should be taken once daily at about 5 PM. If the dose is not taken at the recommended time, the patient should take the next dose at about 5 PM the following day.
- For Postherpetic Neuralgia, the starting dose is 600 mg HORIZANT in the morning for 3 days. Starting on day 4, 600 mg HORIZANT should be taken twice daily. If the dose is not taken at the recommended time, the next dose should be taken at the time of next scheduled dose.
- Patients should be instructed about how to discontinue HORIZANT.

HORIZANT is a registered trademark of GlaxoSmithKline.

Manufactured by:
Patheon Inc.
Research Triangle Park, NC 27709

for:

GlaxoSmithKline
Research Triangle Park, NC 27709

Licensed from:

XenoPort, Inc.
Santa Clara, CA 95051

HZT:XPI

PHARMACIST—DETACH HERE AND GIVE TO PATIENT

_ _

MEDICATION GUIDE
HORIZANT® (ho-ri' zant)
(gabapentin enacarbil)
Extended-Release Tablets

Read this Medication Guide before you start taking HORIZANT and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about HORIZANT?

HORIZANT can cause serious side effects:

1. **Do not drive after taking your dose of HORIZANT until you know how HORIZANT affects you, including the morning after you take your dose. Do not** operate heavy machinery or do other dangerous activities until you know how HORIZANT affects you. HORIZANT can cause sleepiness, dizziness, slow thinking, and can affect your coordination. Ask your healthcare provider when it would be okay to do these activities.
2. **HORIZANT may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

   Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
   - thoughts about suicide or dying
   - attempt to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated
   - new or worse restlessness
   - panic attacks
   - new or worse trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses
   - an extreme increase in activity and talking (mania)
   - other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop HORIZANT without first talking to a healthcare provider. Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

3. **HORIZANT may cause a serious or life-threatening allergic reaction** that may affect your skin or other parts of your body such as your liver or blood cells. You may or may not have rash with these types of reactions. Call a healthcare provider right away if you have any of the following symptoms:
   - skin rash
   - hives
   - fever
   - swollen glands that do not go away
   - swelling of your lips or tongue
   - yellowing of your skin or eyes
   - unusual bruising or bleeding
   - severe fatigue or weakness
   - unexpected, severe muscle pain
   - frequent infections

These symptoms may be the first signs of a serious reaction. A healthcare provider should examine you to decide if you should continue taking HORIZANT.

What is HORIZANT?

HORIZANT is a prescription medicine used to treat adults with:

- moderate-to-severe primary Restless Legs Syndrome (RLS).
- pain from damaged nerves (postherpetic pain) that follows healing of shingles (a painful rash that comes after a herpes zoster infection).

HORIZANT is not for people with RLS who need to sleep during the daytime and need to stay awake at night.

HORIZANT is not the same medicine as gabapentin (for example, NEURONTIN® or GRALISE®) and should not be used in its place.

It is not known if HORIZANT is safe and effective in children.

What should I tell my healthcare provider before taking HORIZANT?

Before taking HORIZANT, tell your healthcare provider if you:

- have or have had kidney problems or are on hemodialysis.
- have or have had depression, mood problems, or suicidal thoughts or behavior.
- have or have had seizures.
- have a history of drug abuse
- have any other medical conditions
- if you are pregnant or plan to become pregnant. It is not known if HORIZANT will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant while taking HORIZANT. You and your healthcare provider will decide if you should take HORIZANT while you are pregnant.
- are breastfeeding or plan to breastfeed. Your body turns HORIZANT into another drug (gabapentin) that passes into your milk. It is not known if this can harm your baby. You and your healthcare provider should decide if you will take HORIZANT or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take HORIZANT?

- Take HORIZANT exactly as your healthcare provider tells you to take it. Your healthcare provider will tell you how much HORIZANT to take and when to take it.
- Take HORIZANT tablets whole. **Do not** cut, crush, or chew your tablet.
- Take HORIZANT tablets with food.
- **Do not stop taking HORIZANT without talking to your healthcare provider first.** If you stop taking HORIZANT suddenly, you may develop side effects.
- If you forget to take your medicine at the time recommended by your healthcare provider, just skip the missed dose. Take the next dose at your regular time. **Do not** take 2 doses at one time.
- If you take too much HORIZANT, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking HORIZANT?

- Do not take other medicines that make you sleepy or dizzy while taking HORIZANT without first talking with your healthcare provider. Taking HORIZANT with medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not take other gabapentin drugs (for example, NEURONTIN or GRALISE) while you take HORIZANT.

What are the possible side effects of HORIZANT?

- See **"What is the most important information I should know about HORIZANT?"**

The most common side effects of HORIZANT include:

- sleepiness
- dizziness
- headache

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of HORIZANT. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store HORIZANT?

- Store HORIZANT between 59° and 86°F (15° and 30°C).
- Keep HORIZANT dry and away from moisture.
- Keep HORIZANT tightly closed in the bottle provided to you. Do not remove any moisture control packs that may come in the bottle.

Keep HORIZANT and all medicines out of the reach of children.

General Information about the safe and effective use of HORIZANT

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use HORIZANT for a condition for which it was not prescribed. Do not give HORIZANT to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about HORIZANT. If you would like more information, talk with your healthcare provider.

You can ask your healthcare provider or pharmacist for information about HORIZANT that was written for healthcare professionals.

For more information about HORIZANT, go to www.gsk.com or call 1-888-825-5249.

What are the ingredients in HORIZANT?

Active ingredients: gabapentin enacarbil
Inactive ingredients: Both the 300 mg and 600 mg tablets contain colloidal silicon dioxide, dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium stearate, sodium lauryl sulfate, and talc. The 300 mg tablets also contain red ferric oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Patheon Inc.
Research Triangle Park, NC 27709

for:

GlaxoSmithKline
Research Triangle Park, NC 27709

Licensed from:

XenoPort, Inc.
Santa Clara, CA 95051

Revised: June 2012

HZT:XMG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-399/S-003

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	June 6, 2012
From	Rigoberto Roca, MD
Subject	Deputy Division Director Summary Review
NDA / Supplement No.	022399 / S-003
Applicant Name	GlaxoSmithKline
Date of Submission	August 9, 2011
PDUFA Goal Date	June 9, 2012
Proprietary Name / Established (USAN) Name	Horizant / gabapentin enacarbil extended release
Dosage Forms / Strength	Oral tablet / 600 mg
Proposed Indication(s)	Management of postherpetic neuralgia
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Robert Levin, MD
CDTL Review	Frank Pucino, PhD, MPH
Statistical Review	Katherine Meaker, MS / Dionne Price, PhD
Pharmacology Toxicology Review	Armaghan Emami, PhD / Adam Wasserman, PhD
ONDQA Review	Bartholome Ho, PhD / James Vidra, PhD
Clinical Pharmacology Review	Wei Qiu, PhD / Yun Xu, PhD Li Zhang, PhD / Atul Bhattaram, PhD
OMPI/DMPP	Sharon Mills, BSN, RN, CCRP/ LaShawn Griffiths, MSHS-PH, BSN, RN / Barbara Fuller, RN, MSN, CWOCN
OPDP/DPDP	Sam Skariah, PharmD / Lisa Hubbard, PharmD
OPDP/DCDP	L. Shenee Toombs, PharmD / Shefali Doshi, MD
OSI/DGCPC	Jean Mulinde, MD / Susan Leibenhaut, MD
Controlled Substances Staff	Stephen Sun, MD / Michael Klein, PhD

CDTL = Cross-Discipline Team Leader
DCDP = Division of Consumer Drug Promotion
DGCPC = Division of Good Clinical Practice Compliance
DPDP = Division of Professional Drug Promotion
DMPP = Division of Medical Policy Programs

OMPI = Office of Medical Policy Initiatives
OND = Office of New Drugs
ONDQA = Office of New Drug Quality Assessment
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology
OSI = Office of Scientific Investigation

1. Introduction

The applicant has submitted a supplemental application with a single adequate and controlled clinical trial to add the following indication to their new drug application (NDA): management of postherpetic neuralgia. It is a 505(b)(2) application, as it is relying in part on the Agency's previous findings of safety and efficacy of Neurontin® (gabapentin), NDA 020235, which is currently approved for the same indication.

This review will provide an overview of the regulatory and scientific facts of this supplemental application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling modifications requested by the Applicant.

2. Background

Postherpetic neuralgia is a painful neuropathic condition that occurs following a herpes zoster infection, which is also known as "shingles." It is the most common complication of herpes zoster, manifesting as pain along cutaneous nerves persisting more than three to four months after the onset of the rash [Desmond RA, et al., J Pain Symptom and Management, 2002; Dworkin RH, Portenoy RK, Pain,1996; Jung BF, Johnson RW, Griffin DR, Dworkin RH, Neurology, 2004].

Although the symptoms of postherpetic neuralgia may be self-limited, patients may experience unrelenting burning, sharp, and/or stabbing pain that can be disabling and last for prolonged time periods (months to years). The risk for postherpetic neuralgia increases with the subject's age, with 68% of cases occurring in patients who are 50 years old or older [Yawn BP, et al, Mayo Clinic Proceedings, 2007].

The following products are currently approved for the treatment of neuropathic pain associated with postherpetic neuralgia:

1) Neurontin (gabapentin tablets and solution)
2) Gralise (gabapentin extended-release tablets)
3) Lyrica (pregabalin capsules and oral solution)
4) Qutenza (capsaicin 8% topical patch)
5) Lidoderm (lidocaine 5% topical patch)

The mechanisms of action of these products in the management of postherpetic neuralgia have not been clearly elucidated. Gabapentin and pregabalin bind to the α2δ subunit of voltage-activated calcium channels, potentially altering calcium channel trafficking and/or calcium currents involved in nociception; since Horizant is a prodrug of gabapentin, its mechanism of action is presumed to be similar. Capsaicin's analgesic properties may result from desensitization of the nerve endings through a reduction of transient receptor potential vanilloid 1 receptor (TRPV1)-expressing nociceptive nerve endings. Lidocaine is an amide anesthetic agent that stabilizes neurons by decreasing neuronal permeability to sodium ions.

Horizant was approved for the treatment of moderate to severe primary restless legs syndrome in adults on April, 6, 2011. The approved dose for this indication is 600 mg once daily, taken with food in the late afternoon (around 5:00 pm).

The regulatory history and the series of the interactions with the Applicant prior to the submission are well summarized in the reviews by Dr. Levin and Dr. Pucino. During the pre-NDA meeting for this supplemental application, several issues were discussed with the applicant with respect as to what would be needed to be included in the submission. During that meeting, the Applicant was informed that, if they could demonstrate that Horizant's systemic exposure is primarily gabapentin and not the prodrug, then only one adequate and well-controlled clinical trial would be required.

3. Chemistry, Manufacturing, and Controls (CMC)

There were no CMC changes proposed in this supplemental application, so the ONDQA reviewers did not have any data that needed to be reviewed.

General Product Considerations

From Dr. Ho's and Dr. Vidra's review, they noted that the description in the label noted the following about the product:

> HORIZANT (gabapentin enacarbil) is a prodrug of gabapentin. Gabapentin enacarbil is described as (1-{[({(1*RS*)-1-[(2-Methylpropanoyl)oxy]ethoxy} carbonyl)amino]methyl} cyclohexyl) acetic acid. It has a molecular formula of C16H27NO6 and a molecular weight of 329.39. It is a racemate.
>
> Gabapentin enacarbil is a white to off-white crystalline solid with a melting onset of approximately 64°C and a solubility of 0.5 mg/mL in water and 10.2 mg/mL in phosphate buffer (pH 6.3).
>
> HORIZANT is administered orally. Each HORIZANT Extended-Release Tablet contains 300 mg or 600 mg of gabapentin enacarbil and the following inactive ingredients: colloidal silicon dioxide, dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium stearate, sodium lauryl sulfate, and talc. The 300 mg tablets also contain red ferric oxide.

Stability testing supports an expiry of 36 months at 25°C (77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F). The Applicant performed an environmental assessment and requested a categorical exclusion, which was deemed acceptable. There are no outstanding issues.

Facilities Review/Inspections

There was no need to have facilities inspected for the purposes of this supplemental application.

Outstanding or Unresolved Issues
I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance.

4. Nonclinical Pharmacology/Toxicology

General Considerations
The nonclinical development program that supported the original NDA for the treatment of restless leg syndrome had data intended to support oral administration of gabapentin enacarbil at a dose of up to 1200 mg per day. The same drug substance and drug product approved in the original NDA is being proposed by the Applicant for this supplemental NDA; therefore, the pharmacology/toxicology reviewers determined that additional nonclinical studies were not necessary to support this application.

The assessment of the results of the nonclinical development program by the review team for the initial application generally supported this supplemental application. The only issues that required re-evaluation by this division's pharmacology/toxicology reviewers were the findings of pancreatic tumors in the rats, and ensuring that the label adequately reflected the exposure information, since the proposed dosage regimen for the management of postherpetic neuralgia is different than the approved dosage regimen for the treatment of restless leg syndrome.

Carcinogenicity
As noted by Dr. Emami in her review, the toxicology review of the original NDA for the treatment of restless legs syndrome identified pancreatic tumors in the rat, resulting in a complete response due to an inadequate safety margin. The Applicant addressed the concerns by noting that the same tumor findings had been identified in gabapentin, to which the applicant was referring as part of their 505(b)(2) application. The Applicant provided new data in the submission addressing the deficiencies identified in the Complete Response letter, assessing the plasma exposure to gabapentin under similar conditions as what was used in the gabapentin enacarbil nonclinical studies. The Applicant was able to demonstrate that the exposure to gabapentin in the rat with 1000 mg/kg of gabapentin was approximately 25 times higher than the human exposure, and intermediate between the exposures observed at 500 and 2000 mg/kg of gabapentin enacarbil. The application for the restless leg syndrome indication was approved as it was deemed that a 25-fold margin was acceptable.

For the indication being requested in this supplemental application, the maximum recommended dose is 1200 mg per day, twice of what was approved for the treatment of restless leg syndrome; therefore, the exposure margin has decreased by about 50%. This would indicate that the NOAEL for the pancreatic tumors observed in the rats occurs at an exposure to gabapentin that is ~13-fold higher than the clinical exposure. Dr. Emami and Dr. Wasserman noted that the potential carcinogenic risk of the proposed drug product is likely reduced, comparatively speaking, because postherpetic neuralgia does not generally require long-term treatment (i.e., longer than 6 months). Their conclusion

was that a 13-fold margin was acceptable for this indication, and recommended approval of the supplemental application from a pharmacology/toxicology perspective.

Outstanding or Unresolved Issues

I concur with the conclusions reached by Dr. Emami and Dr. Wasserman that there are no outstanding pharmacology/toxicology issues that would preclude approval of this supplemental application.

5. Clinical Pharmacology/Biopharmaceutics

General Considerations

Horizant is an extended release formulation of gabapentin enacarbil, a prodrug of gabapentin. As noted in Dr. Qiu's review of May 3, 2012, the clinical and clinical pharmacology database that supports this supplemental application consists of 17 clinical pharmacology studies, one population PK/PD assessment, a modeling-simulation evaluation for renally impaired patients, and 3 clinical trials. The vast majority of these data were previously reviewed by the Division of Psychiatry Products during their evaluation of the original NDA, or in subsequent submissions.

The data reviewed for this supplemental application consisted of the modeling-simulation for patients with renal impairment and the data from the clinical trials in patients with postherpetic neuralgia. Dr. Qiu's review notes three major clinical pharmacology findings in pertinent for this supplemental application:

- Steady state gabapentin exposure at the recommended HORIZANT dose of 1200 mg/day is predicted to be between the gabapentin exposure of Neurontin from 900 mg/day to 1800 mg/day, the recommended therapeutic dose range for Neurontin.
- Blood levels of the pro-drug gabapentin enacarbil are low and transient (≤ 2% of corresponding gabapentin plasma levels).
- Proposed dosing regimen for HORIZANT in Postherpetic Neuralgia patients with varying degrees of renal function is acceptable. However, the proposed dosing guidelines for End-Stage Renal Disease (ESRD) groups of renal impaired patients are not acceptable. Given the fact that ESRD subjects will have varying dialysis times, and potentially varying HORIZANT dosing schedules, there is no dosing and dialysis scenario that is practically possible that would provide a profile in all ESRD subjects that never exceeds the exposures in normal subjects Thus, this product is not recommended for Postherpetic Neuralgia patients with ESRD.

Pharmacokinetics of Horizant

Dr. Qiu's review notes the following regarding the pharmacokinetics of Horizant.

Absorption:
The absorption of gabapentin enacarbil is via an active transport by a proton-linked monocarboxylate transporter, MCT-1, expressed at high levels in the intestinal tract. After oral administration, gabapentin enacarbil undergoes extensive first-pass hydrolysis by non-specific carboxylesterases primarily in enterocytes and to a lesser extent in the liver, to form gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid. Levels of gabapentin enacarbil in blood are low and transient (≤ 2% of corresponding gabapentin plasma levels). The extended exposures to gabapentin increase in an approximate dose-proportional manner over the range of 300 to 6000 mg. Based on urinary recovery of gabapentin, mean bioavailability of gabapentin is from 42% to 65% under fasting condition and about 75% under fed condition. The exposure of gabapentin was increased by 24%, 34%, and 44% by low, moderate, and high fat meals, respectively. The T_{max} of gabapentin was 5 hours in fasted subjects and 7.3 hours in fed subjects. Steady state is reached in 2 days with daily administration.

Distribution:
Plasma protein binding of gabapentin is less than 3%. The apparent volume of distribution of gabapentin is 76 L.

Metabolism:
Gabapentin is not apparently metabolized in humans. Neither gabapentin enacarbil nor gabapentin are substrate, inhibitors, or inducers of the major cytochrome P450 enzymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4). Gabapentin enacarbil is neither a substrate nor an inhibitor of P-glycoprotein in vitro.

Elimination/Excretion:
Gabapentin is excreted unchanged by the kidney and is believed to involve a component of active secretion via an organic cation transporter (OCT2). The elimination half-life of gabapentin ranges from 5.1 to 6 hours and is unaltered by dose or following multiple dose administration.

Critical Intrinsic Factors
Age:
The clinical trials in patients with postherpetic neuralgia included approximately 100 patients older than 65 years of age, and no overall differences were noted in the safety or effectiveness between these patients and younger patients. However, since older patients are more likely to have decrease renal function, and Horizant is almost exclusively excreted by the kidney, dose adjustments may be needed. This observation is already noted in the currently approved package insert.

Renal impairment:
As noted above, clearance is decreased in patients with renal impairment, and the Applicant has proposed a scheme for dose modification based on a patient's renal function and it has been found to be acceptable.

It is noted that the original assessment by the clinical pharmacology team was that Horizant was not to be recommended for patients on hemodialysis, as no dosing scheme could be identified that would yield a comparable exposure profile consistent with what was observed with patients with restless leg syndrome.

After additional internal discussions, the review team concluded that, as noted in Dr. Zhang's amendment on May 17, 2012, patients with postherpetic neuralgia would benefit from sustained therapeutic concentrations throughout the day, whereas patients with restless leg syndrome need therapeutic concentrations to be present predominantly during the evening and overnight. Taking into account the differences between the two clinical conditions, and based on the model-simulations provided by the Applicant, the proposed dosing guidelines of having the patients take 300 mg after every dialysis (and increasing to 600 mg after every dialysis, if needed), were deemed acceptable.

Hepatic impairment:
Since gabapentin is not significantly metabolized by CYP enzymes, a specific study in subjects with hepatic impairment has not been conducted; no dosage adjustment based on hepatic function is needed or recommended.

Drug-drug Interactions
Dr. Qui's review noted that Dr. Vaneeta Tandon's reviewed the results of an in vitro study conducted by the Applicant to evaluate the potential for dose dumping when Horizant was taken with alcohol, as part of the postmarketing requirements issued when the original application was approved in 2011. The results demonstrated that the modified release characteristics of the formulation were disrupted in the presence of alcohol, with approximately 63% of the gabapentin enacarbil dose being released within 1 hour when taken concomitantly with 40% alcohol (the highest concentration assessed).

The Applicant's interpretation of the results of the in vitro study was that the gabapentin exposure would have been comparable to a combination of a 60% immediate-release/40% extended-release formulation, by utilizing data from two separate clinical pharmacology studies which evaluated these two formulations. The Applicant's simulations predicted that the exposure would have been within the exposure range of the 600 mg extended-release tablets and, therefore, the rapid release at 1 hour posed no safety concerns.

Dr. Tandon's evaluation noted that simulations could not predict the worst case scenario, in part because the study from which the immediate-release data were being derived from used an earlier iteration of the immediate-release formulation. In the absence of clinical data to assess the effects of the shift in exposure, Dr. Tandon's recommendation was that

the Applicant should be asked to submit a labeling supplement to modify the labeling to indicate that alcohol intake should be restricted when taking Horizant.

Pharmacodynamics of Horizant

Thorough QT Study

A thorough QT study was submitted with the original application. The results were inconclusive and the Division of Neurology Products requested that the thorough QT study be repeated as a post-marketing requirement when the application was approved for the restless leg syndrome indication. A protocol for the new study was submitted to the NDA in August, 2011.

Outstanding or Unresolved Issues

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Horizant is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical-Efficacy

The clinical development program conducted in support of this supplemental application consisted of three clinical trials: a 2-week proof-of-concept trial, an 8-week crossover trial, and a 12-week randomized, parallel group, controlled trial. The trials' key features are summarized in the table below (adapted from Dr. Levin's and Dr. Pucino's review).

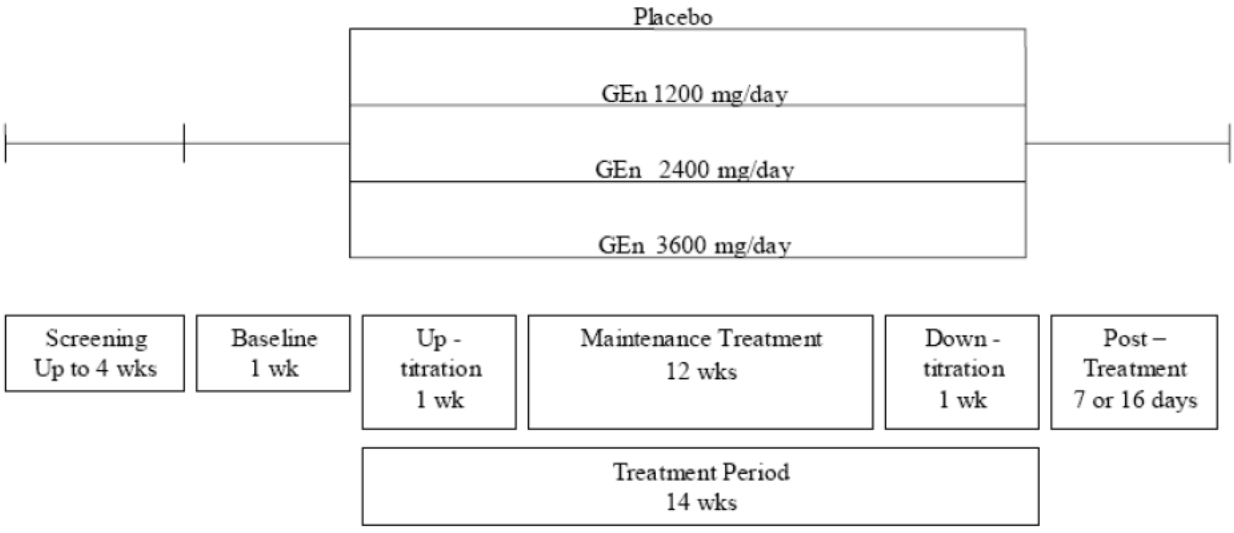
Study Identifier	Study Design	Treatment Duration	Treatment Group	Number of Patients n (Male/Female)
XP009	Randomized Double-blind Placebo-controlled Parallel-group Proof-of-Concept	2 weeks	**Horizant** 1200 mg/d **Placebo**	47 (22/25) 54 (27/27)
PXN110527	Randomized Double-blind 2-period cross-over	8 weeks	**Horizant** 3600 mg/d **Horizant** 1200 ng/d	94 (57/36)

Study Identifier	Study Design	Treatment Duration	Treatment Group	Number of Patients n (Male/Female)
PXN110748	Randomized Double-blind Placebo-controlled Parallel group	12 weeks	**Horizant** 1200 mg/d 2400 mg/d 3600 mg/d **Placebo**	276 (139/137) 107 (53/54) 82 (47/35) 87 (39/48) 95 (50/45)

As mentioned in the background section of this memorandum, the Applicant had been advised at the pre-NDA meeting that, if the data indicated that the systemic exposure with Horizant is primarily gabapentin and not the prodrug, then the Applicant might be able to reference the studies from the listed drug relied upon for approval (i.e., gabapentin), which would result in only needing one adequate and well-controlled trial to support the application. Study PXN110748 represented that clinical trial.

Study PXN110748: *An efficacy and safety study of XP13512 compared with a concurrent placebo control in subjects with neuropathic pain associated with postherpetic neuralgia (PHN).*

As noted in Dr. Levin's review, the overall design of the trial consisted of multicenter, randomized, double-blind, parallel group, placebo-controlled study, and it evaluated the efficacy and safety of three doses of Horizant in subjects with neuropathic pain associated with PHN. The trial consisted of 6 phases: screening (up to 28 days); baseline, including randomization (7 days); up-titration (7 days); maintenance treatment at a fixed dose (12 weeks); down-titration (7 days); and post-treatment follow-up (7 days after the last dose or 16 days in the case of females of childbearing potential). The figure below is a representation of the different phases of the trial, reproduced from the Clinical Study Report.



Eligibility criteria included a diagnosis of PHN for at least three months and a baseline 24-hour average pain intensity score of ≥ 4.0 on an 11-point numerical rating scale (where 0 = "no pain" and 10 = "pain as bad as you can imagine"). The baseline score was calculated as the mean of at least four daily scores during the 7 days prior to randomization. Eligible subjects were randomized in a ratio of 1:1:1:1 to receive:

- Horizant 3,600 mg/day
- Horizant 2,400 mg/day
- Horizant 1,200 mg/day
- Placebo

Endpoints:
The primary endpoint was the change from baseline in the 24-hour average pain intensity, which was recorded in a daily diary and measured on an 11-point Numerical Rating Scale. Secondary endpoints included Patient Global Impression of Change, amount of rescue medication used, average pain during daytime and nighttime, worst pain during daytime and nighttime, amount of pain upon walking, pain at bedtime, sleep interference, and Clinician Global impression of change. None of the secondary endpoints were being considered for inclusion in the label, therefore, there were no statistical adjustments made for multiplicity.

Summary of Efficacy Findings**:**
The trial was conducted at 72 sites in the United States and Canada between February 2008 and July 2009.

The table below, adapted from the Ms. Meaker's statistical review, summarizes the patient disposition for the trial.

	Placebo	**Horizant 1200mg**	**Horizant 2400mg**	**Horizant 3600mg**
Randomized	95	107	84	90
Received Treatment = Intent-to-Treat (ITT)	95 (100%)	107 (100%)	82 (100%)	87 (100%)
Completed up-titration phase	89 (94%)	103 (96%)	79 (96%)	81 (93%)
Completed maintenance phase	65 (67%)	87 (79%)	61 (73%)	57 (64%)
Discontinued during Titration Phase:	6 (6%)	4 (4%)	5 (6%)	9 (10%)
Reason				
Adverse event	4 (4%)	3 (3%)	3 (4%)	3 (3%)
Lack of efficacy	0	0	0	1 (1%)
Subject withdrew consent	0	1 (1%)	0	1 (1%)
Protocol Deviation	2 (2%)	0	1 (1%)	4 (5%)
Investigator discretion	0	0	1 (1%)	0
Discontinued during Maintenance Phase:	24 (25%)	16 (15%)	18 (22%)	24 (28%)
Reason				
Adverse event	7 (7%)	3 (3%)	9 (11%)	13 (15%)

	Placebo	Horizant 1200mg	Horizant 2400mg	Horizant 3600mg
Lack of efficacy	6 (6%)	1 (1%)	1 (1%)	3 (3%)
Subject withdrew consent	5 (5%)	5 (5%)	4 (5%)	3 (3%)
Protocol Deviation	3 (3%)	3 (3%)	3 (4%)	4 (4%)
Investigator discretion	2 (2%)	2 (2%)	1 (1%)	0
Lost to follow-up	1 (1%)	2 (2%)	0	1 (1%)
Discontinued after maintenance phase	1 (1%)	2 (2%)	1 (1%)	1 (1%)

The table below summarizes the demographic and baseline characteristics of the patients who were randomized and who received treatment, i.e., the intent-to-treat population (adapted from Ms. Meaker's review). There were no significant imbalances noted between the treatment groups.

	Placebo N=95	Horizant 1200 mg N=107	Horizant 2400 mg N=82	Horizant 3600 mg N=87	Total N=371
Age (y)					
Mean (SD)	61.7 (12.77)	61.7 (12.58)	64.1 (8.94)	61.3 (15.41)	62.1 (12.67)
Median	64.0	65.0	65.0	63.0	64.0
Range	18 – 83	18 – 87	21 – 83	20 – 92	18 – 92
Age Group, n (%)					
≤65 yrs	53 (56)	62 (58)	47 (57)	47 (54)	209 (56)
>65 yrs	42 (44)	45 (42)	35 (43)	40 (46)	162 (44)
Gender, n (%)					
Female	45 (47)	54 (50)	35 (43)	48 (55)	182 (49)
Male	50 (53)	53 (50)	47 (57)	39 (45)	189 (51)
Ethnicity, n (%)					
Hispanic/Latino	13 (14)	10 (9)	7 (9)	9 (10)	39 (11)
Not Hispanic/Latino	82 (86)	97 (91)	75 (91)	78 (90)	332 (89)
Race, n (%)					
White	79 (84)	94 (89)	69 (85)	73 (84)	315 (86)
African American/African Heritage	14 (15)	11 (10)	8 (10)	11 (13)	44 (12)
American Indian or Alaska	0	0	2 (2)	1 (1)	3 (<1)
Asian	1 (1)	1 (<1)	2 (2)	1 (1)	5 (1)
Japanese/East Asian Heritage/South East Asian Heritage	0	1 (<1)	1 (1)	1 (1)	3 (<1)
Central/South Asian Heritage	1 (1)	0	1 (1)	0	2 (<1)
Native Hawaiian or other Pacific Islander	0	0	0	1 (1)	1 (<1)
BMI (kg/m2), n (%)					
≤30	57 (60)	62 (58)	46 (57)	56 (64)	221 (60)
>30	38 (40)	45 (42)	35 (43)	31 (36)	149 (40)
Baseline 24-hour average pain score, n (%)					
4 – < 6.5	56 (59)	63 (59)	58 (71)	47 (54)	224 (60)

	Placebo N=95	Horizant 1200 mg N=107	Horizant 2400 mg N=82	Horizant 3600 mg N=87	Total N=371
6.5 – 10	39 (41)	44 (41)	24 (29)	40 (46)	147 (40)
Baseline 24-hour average pain score					
Mean (SD)	6.33 (1.370)	6.28 (1.525)	5.98 (1.569)	6.47 (1.579)	NA
Range	4.1 – 9.4	4.0 – 10	4.0 – 9.8	4.0 – 10.0	NA

Result of the Primary Efficacy Endpoint

As noted in Ms. Meaker's review, the primary endpoint was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, center, baseline pain, and body mass index. Each of the treatment groups of Horizant were compared to placebo, with a Dunnett's test to maintain an overall alpha level of 0.05, which was considered acceptable. The analyses were performed on the intent-to-treat population, defined as all randomized patients who received at least one dose of study treatment and who had at least one post-baseline assessment.

The Applicant intended to use the last observation carried forward (LOCF) approach to impute missing data. This was discussed with the Applicant during the pre-sNDA meeting, particularly noting that this approach had the potential to impute a good outcome for a patient who had discontinued due to adverse events. At that meeting, the Applicant indicated that they would also provide an efficacy analysis which would use a baseline observation carried forward (BOCF) approach. In addition, the Applicant included an analysis in the submission that utilized a Hybrid BOCF/LOCF, which imputed a baseline value for any missing weeks on treatment if a patient discontinued due to an adverse event, and a last observation value if the patient discontinued for any other reason.

The results of these analyses are summarized in the table below, adapted from Ms. Meaker's review, as well as the results of the Observed Cases analyses, which was a "completer's analysis" (i.e., a patient had to have pain scores during the final study week in order to be included in the analysis).

	Placebo N=95	Horizant 1200 mg N=107	Horizant 2400 mg N=82	Horizant 3600 mg N=87
Baseline				
n	95	107	82	87
Mean (SD)	6.33 (1.370)	6.28 (1.525)	5.98 (1.569)	6.47 (1.579)
Change from Baseline to Week 13 (LOCF)				
n	95	106	80	87
Adjusted Mean (SE)[1]	-1.66 (0.216)	-2.47 (0.204)	-2.36 (0.237)	-2.72 (0.227)
Adjusted Mean Difference vs. Placebo[2]		-0.81	-0.70	-1.07
95% CI		(-1.40, -0.23)	(-1.33, -0.07)	(-1.68, -0.45)
p-value Adjusted for		0.013	0.029	0.002

	Placebo N=95	Horizant 1200 mg N=107	Horizant 2400 mg N=82	Horizant 3600 mg N=87
Multiplicity[3]				
Unadjusted p-value[4]		0.007	0.029	0.001
Change from Baseline to Week 13 (BOCF)				
n	95	107	81	87
Adjusted Mean (SE)[1]	-1.32 (0.213)	-2.25 (0.200)	-1.97 (0.232)	-2.00 (0.223)
Adjusted Mean Difference vs. Placebo[2]		-0.94	-0.65	-0.68
95% CI		(-1.51, -0.36)	(-1.27, -0.03)	(-1.28, -0.08)
Unadjusted p-value[4]		0.001	0.040	0.027
Change from Baseline to Week 13 (Hybrid BOCF/LOCF)				
n	95	107	81	87
Adjusted Mean (SE)[1]	-1.59 (.220)	-2.33 (.207)	-2.10 (.240)	-2.24 (.231)
Adjusted Mean Difference vs. Placebo[2]		-0.74	-0.51	-0.65
95% CI		(-1.33,-0.15)	(-1.14, 0.13)	(-1.27, -0.03)
Unadjusted p-value[4]		0.014	0.119	0.040
Change from Baseline to Week 13 (Observed Cases)				
n	94	103	80	86
Adjusted Mean (SE)[1]	-1.64 (.218)	-2.50 (.208)	-2.36 (.238)	-2.72 (.228)
Adjusted Mean Difference vs. Placebo[2]		-0.86	-0.72	-1.08
95% CI		(-1.45, -0.27)	(-1.35, -0.09)	(-1.70, -0.47)
Unadjusted p-value[4]		0.004	0.025	0.001

[1] The Adjusted Mean and SE are based on an ANCOVA model adjusted for BMI, baseline 24-hour average pain intensity and grouped center.

[2] A negative treatment difference indicates benefit, relative to placebo.

[3] Adjustments to p-values were made based on multiple treatment arms compared vs. placebo. A step-down procedure that uses Dunnett's test within a closed testing scheme for multiple comparisons with a common control was used to maintain the overall experiment-wise alpha level of 0.05 for the comparisons of Horizant vs. placebo.

[4] Unadjusted p-values are provided for descriptive purposes, and were not adjusted for multiple comparisons.

All of these analyses supported the conclusion that a dosing regimen of 1200 mg/day was effective. The results of an analysis of the Patient Global Impression of Change and the mean daily dosage of rescue medications were also consistent with the finding of efficacy for the proposed dosing regimen. Higher doses were associated with an increased incidence of adverse events, and there was no clear evidence that they were more effective than proposed dose of 1200 mg/day.

8. Safety

The primary safety database supporting the supplemental application is comprised of 417 patients exposed to Horizant in three clinical trials, which is summarized in the table above. Due to differences in study designs and durations of treatment, it was not possible to integrate the data across the three clinical trials.

Focusing on Study PXN10748, the breakdown in exposure is summarized in the following table (adapted from a table in Dr. Levin's review, which was a reproduction of a table from the Integrated Safety Summary in the application). The duration of exposure represented the maximum length of treatment, based on the randomized treatment group and including up-titration, maintenance, and down-titration. The categories are mutually exclusive and time periods which including more than a half-day were rounded up to the next whole number before categorizing (e.g., an exposure duration of 14.5 days was placed in the > 14 to ≤ 30 days category while an exposure duration of 14.2 days was placed in the >7 to ≤ 14 days category).

Duration of Exposure	**Number (%) of Subjects**				
	Placebo N = 95	**Horizant 1200 mg/day N = 107**	**Horizant 1200 mg/day N = 82**	**Horizant 1200 mg/day N = 87**	**Horizant All Doses N = 276**
≤ 7 days	4 (4)	3 (3)	3 (4)	6 (7)	12 (4)
> 7 to ≤ 14 days	6 (6)	1 (<1)	4 (5)	4 (5)	9 (3)
> 14 to ≤ 30 days	4 (4)	1 (<1)	6 (7)	6 (7)	13 (5)
> 30 to ≤ 60 days	10 (11)	10 (9)	5 (6)	8 (9)	23 (8)
> 60 to ≤ 90 days	7 (7)	4 (4)	2 (2)	7 (8)	13 (5)
> 90 days	64 (67	82 (82)	62 (76)	56 (64)	206 (75)

Deaths

There were 6 deaths in the entire Horizant drug development program, which consisted of 2,756 patients across different indications and different clinical trials. None of the deaths were among the 566 patients involved in the postherpetic neuralgia trials.

Serious Adverse Events

There were 15 serious adverse events (SAEs) reported in 11 patients in the postherpetic neuralgia program. There were no SAEs in the proof-of-concept study, occurring only in the other two studies (as noted in Dr. Pucino's review):

> *PXN110748.* Twelve SAEs were reported in nine subjects enrolled, of which one subject, allocated to the Horizant 1200 mg/day treatment arm, experienced an SAE of 'coronary artery disease' post-treatment.
>
> *PXN110527.* Two subjects experienced a total of three nonfatal SAEs (hallucination auditory, post-treatment depression, and post-treatment chest pain).

The types of SAEs reported for Study PXN110748 are summarized in the table below, reproduced from Dr. Pucino's review.

System Organ Class Preferred Term	PXN110748			
	Placebo (N=95)	Horizant 1200 mg/d (n=107)	Horizant 2400 mg/d (N=82)	Horizant 3600 mg/d (N=87)
Number of subjects any event	2 (2%)	1 (1%)	4 (5%)	2 (2%)
Nervous System Disorders	0	0	2 (2%)	0
Intracranial aneurysm	0	0	1 (1%)	0
Multiple sclerosis	0	0	1 (1%)	0
Multiple sclerosis relapse	0	0	1 (1%)	0
Gastrointestinal disorders	0	0	0	1 (1%)
Gastritis	0	0	0	1 (1%)
General disorders and administration site conditions	0	0	1 (1%)	0
Chest pain (non cardiac)	0	0	1 (1%)	0
Infections and infestations	0	0	1 (1%)	0
Sinusitis	0	0	1 (1%)	0
Investigations	0	0	1 (1%)	0
Blood pressure increased	0	0	1 (1%)	0
Psychiatric disorders	0	0	1 (1%)	0
Anxiety	0	0	1 (1%)	0
Reproductive system and breast disorders	0	0	0	1 (1%)
Cystocele	0	0	0	1 (1%)
Cardiac disorders	1 (1%)	1 (1%)	0	0
Atrial fibrillation	1 (1%)	0	0	0
Coronary artery disease[1]		1 (1%)		
Injury, poisoning and procedural complications	1 (1%)	0	0	0
Vascular injury	1 (1%)	0	0	0

Common Adverse Events

The most common adverse events reported in Study PXN110748 were dizziness, somnolence and headache, consistent with what was reported in the trials which supported the restless leg syndrome indication. Dizziness and somnolence were also the most commonly reported treatment-emergent adverse events. There was a dose

relationship observed in that the incidence of adverse events increased with the increased dose of Horizant.

Outstanding or Unresolved Issues
The safety profile reported for the trials in patients with postherpetic neuralgia was consistent with what had been previously observed with Horizant; no new safety signal was observed in the proposed patient population.

9. Advisory Committee Meeting

The convening of an advisory committee meeting for discussion of this application was deemed to be unnecessary. This decision was reached in view of the clinical experience with gabapentin and the specific indication being sought in the application, and the lack of any specific issues identified in the application that would warrant discussion at an advisory committee meeting.

10. Pediatrics

The Office of Orphan Products Development designated Horizant as an orphan drug with respect to this indication and, as such, the submission of a pediatric assessment as required by the Pediatric Research Equity Act (PREA) does not apply. Furthermore, Dr. Levin and Dr. Pucino noted in their reviews that the incidence of postherpetic neuralgia in the pediatric patient population is too low, and that clinical trials would not be practicable.

11. Other Relevant Regulatory Issues

Consultations were obtained from the Division of Consumer Drug Promotion and the Division of Professional Drug Promotion. Their recommendations were reviewed and incorporated in the appropriate locations in the package insert and labeling.

Division of Good Clinical Practice Compliance Audits
The Division of Good Clinical Practice Compliance (DGCPC) inspected two clinical sites, primarily based on their relatively high subject enrollment. There were three issues identified by the inspectors:

- Three incidents of failure to follow the protocol-specified exclusion criteria.
- Inability to confirm the individual pain scores that the patients reported and which were subsequently entered into the database because the pain scores were entered directly into an electronic diary and the data was transmitted directly to a third-party vendor. A recent inspection of the third-party vendor by the DGCPC had not identified any regulatory violations, and it was decided that a re-inspection was not necessary.
- The sequence of events accompanied the flow of the data. Specifically, data was collected via electronic case report forms and transmitted to the Applicant. The clinical investigator did not retain a write-protected copy of the electronic case report form but, instead, received a CD directly from the Applicant. This situation raises the possibility of data manipulation; however, comparison of hard

copies of the data at the clinical investigator site with data provided in the data listings did not indicate that the data had been manipulated.

Although the inspections did identify potential issues, the overall impression of the DGCPC was that the data generated by these two clinical sites could be considered reliable and acceptable for use in support of the supplemental application.

Financial Disclosure

The Applicant certified that there was no financial arrangement with the study investigators whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that no listed investigator was the recipient of significant payments of sorts as defined in 21 CFR 54.2 (f). The Applicant also indicated that the clinical investigators were required to disclose to the Applicant whether the investigator had a proprietary interest in the product or a significant equity in the Applicant, as defined in 21 CFR 54.2(b).

Dr. Levin identified one investigator who reported a significant financial interest in the Financial Disclosure form; however, the investigator only enrolled (b) (4) patients (out of 376 patients enrolled in the study, or (b) (4)) and Dr. Levin concluded that this investigator was unlikely to be able to affect the outcome of the entire trial.

Consult from Division of Professional Promotion

The Division of Professional Promotion provided several comments regarding the package insert, and the carton and container labeling. The comments were incorporated as appropriate during the course of the review of the proposed label.

Consult from the Controlled Substances Staff

The Controlled Substances Staff was consulted because Horizant is a CNS-active drug and, as such, may have the potential for abuse. Dr. Sun noted in his review that the FDA had previously conducted a surveillance of gabapentin's postmarketing abuse liability 2004 and that his new review served to update those findings. His evaluation of various sources of information, such as Drug Abuse Warning Network (DAWN), Adverse Event Report System (AERS), American Association of Poison Control Center (AAPCC), Horizant postmarketing experience, literature, and abuse message board postings indicated that, compared to other scheduled drugs, the rate of misuse and abuse appears to be relatively low when considering the large denominator of prescriptions.

Dr. Sun's review also noted various factors which made the abuse potential of gabapentin enacarbil not well understood, and his overall recommendation was for continued surveillance of the misuse and abuse of gabapentin enacarbil (and related products gabapentin and pregabalin) for an additional 2 to 5 years, and to have Horizant's label reflect what is currently known about the abuse and dependence potential.

Outstanding or Unresolved Issues

There are no unresolved relevant regulatory issues that would preclude approval of this supplemental application.

12. Labeling

The Applicant has submitted enough information to support their proposed labeling.

As noted above, representatives from the Division of Medical Policy Programs and the Division of Professional Drug Promotion were consulted and their recommendations were incorporated during the discussion of the label with the Applicant.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval.

Risk:Benefit Assessment

I concur with the review team that the application has provided sufficient to support a finding of effectiveness and that the safety profile of Horizant results in a favorable risk:benefit ratio when the product is used as indicated.

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Commitments

None.

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/s/

RIGOBERTO A ROCA
06/06/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-399/S-003

OFFICER/EMPLOYEE LIST

Officer/Employee list
Application: NDA 022399/s-003

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Emami, Armaghan
Fuller, Barbara
Griffiths, LaShawn
Ho, Bartholome
Klein, Michael
Levin, Robert A.
Mills, Sharon
Price, Dionne
Pucino, Frank
Qiu, Wei
Rappaport, Bob
Roca, Rigoberto
Stradley, Sara
Sun, Stephen
Toombs, LaToya (Shenee)
Turner-Rinehart, Sharon
Wasserman, Adam
Xu, Yun
Zhang, Li

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-399/S-003

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	19 May 2012
From	Frank Pucino, PharmD, MPH, Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 022399 S-003
Applicant	Horizant
Date of Submission	09 August 2011
PDUFA Goal Date	09 June 2012
Proprietary Name / Established (USAN) names	Horizant (Gabapentin Enacarbil)
Dosage forms / Strength	Extended-Release Tablets: 300 and 600 mg
Proposed Indication(s)	Postherpetic Neuralgia (PHN) in Adults
Recommended:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Robert Levin, MD
Statistical Review	Katherine Meaker, MS / Dionne Price, PhD
Pharmacology Toxicology Review	Armaghan Emami, PhD / Adam Wasserman, PhD
Clinical Pharmacology	Wei Qiu, PhD / Yun Xu, PhD
CMC / ONDQA	Bartholome Ho, PhD / James Vidra, PhD
CSS	Stephen Sun, MD / Michael Klein, PhD
DGCPC/OSI	Jean Mulinde, MD / Susan Leibenhaut, MD
DPDP DCDP	Sam Skariah, PharmD / Lisa Hubbard, PharmD L. Shenee Toombs, PharmD / Shefali Doshi, MD
DMPP	Sharon Mills, PhD / LaShawn Griffiths, MSHS-PH, BSN, RN / Barbara Fuller, RN, MSN, CWOCN

Abbreviations: CMC, Chemistry, Manufacturing, and Control; CSS, Controlled Substance Staff; DCDP, Division of Consumer Drug Promotion; DDMAC, Division of Drug Marketing, Advertising and Communication (CDER); DGCPC, Division of Good Clinical Practice Compliance (CDER); DMEPA, Division of Medical Error Prevention and Analysis (CDER); DMPP, Division of Medical Policy Programs; DPDP, Division of Professional Drug Promotion; ONDQA, Office of New Drug Quality Assessment (CDER); OSE, Office of Surveillance and Epidemiology (CDER)

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1. Introduction

Horizant (gabapentin enacarbil), a prodrug of gabapentin, is currently approved for the treatment of moderate-to-severe primary restless legs syndrome (RLS). On 9 August 2011, GlaxoSmithKline (GSK; henceforth referred to as the Applicant) submitted a supplemental New Drug Application (sNDA 022399/S-003) for the following additional indication: management of postherpetic neuralgia (PHN) in adults.

This sNDA is being submitted as a 505(b)(2) application, and will rely in part on previous findings of safety and efficacy for the approved listed drug Neurontin (gabapentin). To support the safety and efficacy of Horizant for the proposed indication, the Applicant submitted the results from a single adequate and well-controlled clinical trial (Phase 2b). Additionally, the Applicant conducted two Phase 2 studies in PHN patient populations, and submitted two published reports that provide evidence of effectiveness of the parent drug, gabapentin, in the treatment of PHN. This review will focus primarily on the adequacy of the data submitted from the Phase 2b efficacy study to support the application. An overview of the regulatory history of this product and issues and concerns related to the efficacy and safety of Horizant for the proposed dose and indication will be presented.

2. Background

Horizant is an oral extended-release prodrug of the active drug substance gabapentin. Compared to gabapentin (tradename Neurontin), Horizant is more readily and completely absorbed from the gastrointestinal (GI) tract. Gabapentin is currently marketed for the treatment of partial seizures (approved in 1993) in adults and children, and for the management of PHN (approved in 2004) in adults. Generic formulations of gabapentin are available, and there is extensive experience with this product worldwide.

On 6 April 2011, Horizant was approved for the treatment of moderate-to-severe primary RLS. The approved dose for this indication is 600 mg once daily, taken with food at 5 PM. The Applicant submitted a sNDA requesting approval of Horizant for the management of PHN in adults on 9 August 2011. The proposed dose for this indication is 600 mg in the morning for the first 3 days followed by a dose increase to 600 mg twice daily beginning on Day 4. There are currently five other products approved in the U.S. for the PHN indication; 1) gabapentin tablets and oral solution (Neurontin); 2) gabapentin extended-release tablets (Gralise); 3) pregabalin capsules and solution (Lyrica); 4) capsaicin 8% topical patch (Qutenza); and 5) lidocaine 5% topical patch (Lidoderm).

A review of the regulatory history for Horizant is discussed in detail in the Clinical Review by Robert Levin, MD, the clinical reviewer for this efficacy supplement. The milestone meetings and regulatory actions for this product, summarized from his review, are depicted in Table 1 below.

Table 1: Milestone Meetings and Regulatory Actions

Regulatory Interactions between the FDA and the Applicant	
Date	**Topics**
1 October 2003	Development program for Horizant (IND 068341) for PHN initiated by XenoPort
13 December 2004	RLS development program conducted under IND 071352
20 April 2007	(b) (4)
17 February 2010	A CR issued for the RLS indication primarily due to preclinical findings of pancreatic acinar cell carcinoma for both Horizant (about an 8-fold safety margin for 600 mg/day) and Neurontin
6 October 2010	The NDA for the RLS indication was resubmitted with additional preclinical data to support a safety margin with the 600 mg/day dose of about 25-fold for pancreatic acinar cell carcinoma
17 March 2011	At the Pre-NDA Meeting for PHN indication, the following issues were discussed with the Applicant: • A sNDA submission is acceptable provided the product is approved for RLS • A 505(b)(2) submission is acceptable but the degree to which the Applicant can rely on information without a right of reference will be a review issue • Pediatric studies are not feasible due to the low incidence of PHN • The nonclinical data appears sufficient to support submission of a sNDA for the 1200 mg/day dose, but will be a review issue • Determination whether the carcinogenicity risk at the 1200 mg/day dose has been adequately addressed is a review issue • The Applicant did not conduct a direct relative BA/BE study to compare the bioavailability of gabapentin between Horizant 600 mg BID and Neurontin 600 mg TID; whether or not the comparison based on extrapolation would be adequate will be a review issue • No additional drug-drug interaction studies would be needed for filing • An additional TQT study is requested as a postmarketing requirement for the RLS indication because the moxifloxacin control group did not elicit the expected change in the QT interval • Provided significant CNS depression is not observed in the PHN development program, potential effects on driving/operating heavy machinery can be addressed in labeling – In support of the RLS NDA, a simulated driving study was conducted in subjects with RLS on Horizant 1200 or 1800 mg once daily • As a 505 (b)(2) application for a prodrug and provided systemic exposure with Horizant is primarily gabapentin and not the prodrug, the Applicant might be able to reference the studies from the listed drug relied upon for approval (i.e., gabapentin), which would result in only needing one additional study • Provide the pooled datasets for all safety data from the double-blind, placebo-controlled studies in PHN • Not integrating safety data from non-PHN studies with PHN studies in the analyses in the ISS appears reasonable
6 April 2011	Horizant is approved for the treatment of moderate-to-severe primary RLS with the following required pediatric assessments and PMRs: • Pediatric PK/PD, efficacy and safety and long-term safety studies in adolescents with RLS • A driving study in adolescent patients with RLS using diphenhydramine as

Regulatory Interactions between the FDA and the Applicant	
	active control • An *in vitro* study to evaluate the potential for Horizant and gabapentin to inhibit CYP2C8 and CYP2B6 • An *in vitro* dissolution study to evaluate alcohol dose dumping effects using the final dissolution method, and evaluate alcohol concentrations up to 40% • A simulated driving trial in healthy adult subjects treated with 600 mg Horizant that includes active comparator and placebo arms • A simulated driving trial in healthy adult subjects treated with an appropriate dose of Horizant (determined in PMC efficacy study of lowest effective dose) that includes active comparator and placebo arms • An adequate, randomized, double-blind, placebo- and moxifloxacin-controlled trial to evaluate effects of Horizant on cardiac repolarization in healthy adult subjects • A clinical drug-drug interaction trial to evaluate the PK/PD interactions between Horizant and morphine The Approval Letter contained the following PMCs: • Develop a dosage form that will allow for a 300 mg dose that could be taken once daily in patients with severe renal impairment, including patients on hemodialysis • Conduct a randomized, placebo-controlled, double-blind, parallel-group clinical trial of Horizant at 300, 450 and 600 mg/day in patients with moderate to severe symptoms of RLS
7 June 2011	Horizant is granted orphan-drug designation in the U.S. (Orphan Drug Designation Request #10-3307) for the management of PHN
9 August 2011	NDA for PHN submitted to DAAAP

Source: Modified from Robert Levin, MD, Clinical Review, Table 2, p. 12.
Abbreviations: BA, bioavailability; BE, bioequivalence; BID, twice daily; CR, complete response; CYP, cytochrome P450; DAAAP, Division of Anesthesia, Analgesia, and Addiction Products; DNP, Division of Neurology Products; GSK, GlaxoSmithKline; IND, Investigational New Drug; ISS, Integrated Summary of Safety; PD, pharmacodynamics; PHN, postherpetic neuralgia; PK, pharmacokinetics; PMC, postmarketing commitment; PMR, postmarketing requirement; RLS, restless leg syndrome; TID, three times daily.

It is important to note that, during the pre-sNDA meeting (17 March 2011) for the PHN development program, the Applicant was told that only one adequate and well-controlled clinical trial may be needed to support the proposed indication as a 505 (b)(2) application for a prodrug of gabapentin. However, this would depend on whether the Applicant could demonstrate that most of the active drug in the systemic circulation was gabapentin and not the prodrug, gabapentin enacarbil.

3. CMC/Device

The Applicant did not submit any CMC changes related to this sNDA. Therefore, the information submitted to the original NDA (i.e., to support approval of Horizant for the treatment of moderate to severe RLS in adults) is applicable.

4. Nonclinical Pharmacology/Toxicology

Dr. Armaghan Emami, the Pharmacology/Toxicology reviewer for this sNDA, acknowledged a previous concern about pancreatic tumors in male Wistar rats observed during the review of the nonclinical data submitted to the RLS NDA. Dr. Emami noted that increases in the incidence of pancreatic acinar adenoma and carcinoma were observed at the 2000 mg/kg dose level of gabapentin enacarbil in male rats, but not at 500 mg/kg dose level. Since the Applicant is relying on the Agency's finding of safety for gabapentin, 1000 mg/kg of gabapentin is considered to be the no-effect dose for the occurrence of carcinoma. Data submitted previously by the Applicant supports that gabapentin exposure in the rat at 1000 mg/kg was approximately 13 times higher than the human exposure to gabapentin at the maximum recommended human dose of gabapentin enacarbil (i.e., 1200 mg/day) and was intermediate between the gabapentin exposures observed with the 500 and 2000 mg/kg gabapentin enacarbil dose levels., Further, since PHN is not considered a chronic medical condition, Dr. Emami felt that the carcinogenic risk of this product is likely limited.

In her review, Dr. Emami noted that the previous nonclinical safety assessment of the RLS NDA supported oral administration of Horizant at daily doses up to 1200 mg. Therefore, she concluded, with concurrence from Dr. Adam Wasserman, that no additional nonclinical studies are necessary to support approval of the current application

5. Clinical Pharmacology/Biopharmaceutics

Horizant is an extended-release formulation of a prodrug of gabapentin, and therefore therapeutic response in the treatment of PHN is attributed to gabapentin. Although gabapentin binds with high affinity to the $\alpha 2\delta$ subunit of voltage-activated calcium channels, the mechanism of action by which gabapentin is efficacious in PHN is unclear.

The bioavailability of gabapentin following oral administration of Horizant is approximately 75%, and gabapentin enacarbil plasma concentrations are less than 2% of corresponding gabapentin plasma concentrations. Dose-proportionality is observed over a 300 to 6000 mg range, and the time to achieve maximum plasma gabapentin concentrations (T_{max}) after a dose is 5 and 7.3 hours in a fasted and fed state, respectively. Gabapentin is eliminated renally, with plasma clearance approximating creatinine clearance (CrCl). The elimination half-life (t½) of gabapentin ranges from 5.1 to 6.0 hours.

The clinical and clinical pharmacology database for this supplemental NDA consists of 17 clinical pharmacology studies, one population PK/PD, one modeling-simulation for renal impaired patients, and 3 Phase 2 studies. Dr. Wei Qiu reviewed the efficacy supplement for this sNDA, and, with concurrence from Dr. Yun Xu, found it acceptable

from a clinical pharmacology perspective. The main clinical pharmacology findings summarized in Dr. Qiu's review are summarized below:

- *The predicted mean steady state C_{max}, AUC_{0-24}, and Cmin values of gabapentin at proposed dosing of 600 mg twice daily are 5.5 ug/mL, 97 ug•hr/mL, and 3.30-4.36 ug/mL, respectively, which are lower than that for Neurontin 600 mg TID and greater than that for Neurontin 300 mg TID.*

- *Blood levels of the prodrug gabapentin enacarbil are low and transient (≤ 2% of corresponding gabapentin plasma levels). The relative exposure ratios (gabapentin enacarbil/gabapentin) calculated as the ratio of the molar C_{max} and AUC values for the two compounds were ≤ 0.25% and ≤ 1.69%, respectively.*

- *The proposed dosing regimen for HORIZANT in PHN patients with varying degrees of renal function is acceptable. Based on simulations, 300 mg dose following every dialysis would allow End Stage Renal Disease (ESRD) patients with 1% or less normal CL/F to achieve concentrations comparable to the reference range (60-120 mL/min); and the concentrations in subjects with 5% or more normal CL/F to be at the lower end of the reference range. Considering PHN patients may need to maintain therapeutic concentration during day and night, the Applicant's proposed dosing guidelines "…300 mg following every dialysis. Increase to 600 mg following every dialysis if needed" for patients with CrCl < 15 mL/min on hemodialysis is acceptable.*

- *Literature data from two publications showed that the C_{max}, AUC_{0-24}, and C_{min} values of gabapentin given Neurontin 300 mg TID are approximately 4.02-4.56 ug/mL, 74.4-94.1 ug•hr/mL, and 2.13 ug/mL, respectively*.

I concur with the Clinical Pharmacology review team that no additional clinical pharmacology or biopharmaceutics data are required for approval of this sNDA application. For further details related to clinical pharmacology of Horizant refer to Dr. Qiu's Clinical Pharmacology Review (3 May 2012) and the 17 May 2012 Addendum.

6. Clinical Microbiology

Since Horizant is not a therapeutic antimicrobial, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical - Efficacy

The primary clinical review was conducted by Dr. Levin, and the primary statistical review was conducted by Katherine Meaker, MS. with concurrence from Dionne Price, PhD.

As noted above, the Applicant submitted one adequate and well-controlled clinical trial, Study PXN110748, to support the efficacy and safety of Horizant for the management of PHN in adults. Below is a description of this study and the respective efficacy findings. Detailed description and discussion are presented in the Statistical and Clinical reviews by Katherine Meaker, MS and Robert Levin, MD, respectively.

STUDY NA/PXN110748

Title: Study PXN110748: An efficacy and safety study of XP13512 (Horizant) compared with a concurrent placebo control in subjects with neuropathic pain associated with postherpetic neuralgia (PHN)

Objective: To investigate the efficacy of Horizant to reduce pain, improve physical and emotional function, and to assess global improvement, and to evaluate its safety

Design: Randomized, double-blind, placebo-controlled, parallel arm, multicenter Phase 3 study

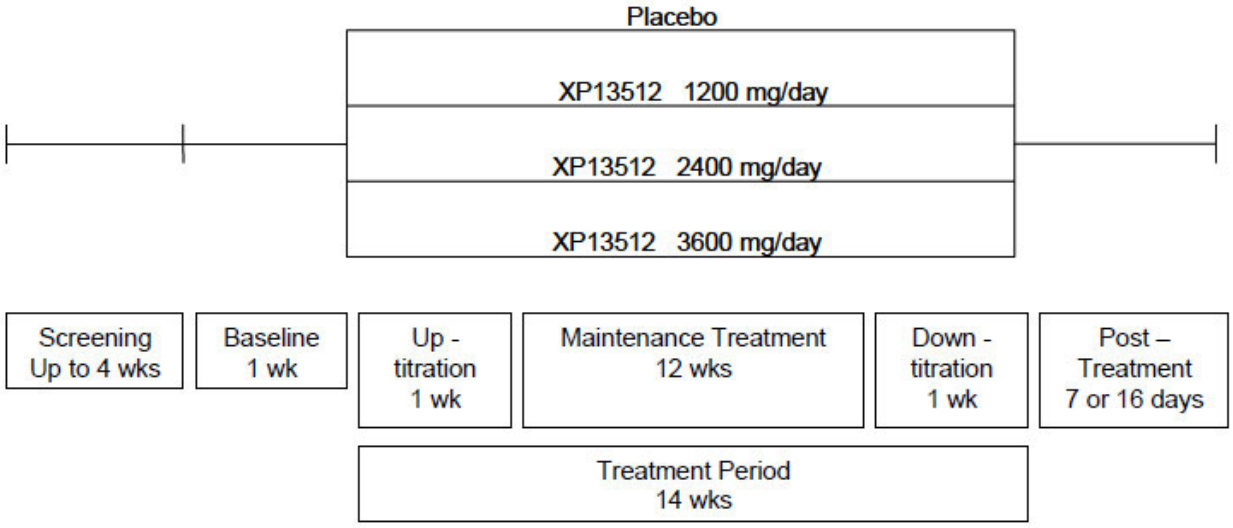
Duration: 21 weeks (screening, baseline, double-blind and post-treatment study phases)

Setting: 72 centers in the United States and Canada

Patients: 376 patients (enrolled from 6 February 2008 through 29 July 2009)

Intervention: Randomized in a 1:1:1:1 allocation scheme to receive either Horizant (600, 1200 or 1800 mg BID) or placebo (Figure 1).

Figure 1: Study Design Diagram



Source: Clinical Study Report, PXN110748, Figure 1, p. 18.

Primary Efficacy Endpoint: Percent change from baseline (i.e., during the 7 days prior to randomization) in the average pain intensity (i.e., 11-point numeric rating scale [NRS]) for the past 24 hours during Weeks 2 through 12.

Secondary Efficacy Endpoints:

- Percent of subjects achieving 10%, 20%, 30%... reduction in the 24-hour average pain intensity
- Time to onset of sustained improvement in the 24-hour average pain intensity defined as a reduction of ≥ 2 points from baseline for ≥ 2 consecutive days
- Day-time average pain intensity score recorded in the evening before bedtime and defined as the time between rising in the morning and going to bed at night
- Night-time average pain intensity score recorded in the morning upon awakening and defined as the time between going to bed at night and rising in the morning
- Current pain intensity score recorded in the morning upon awakening and in the evening before bedtime
- Day-time worst pain intensity score recorded in the evening before bedtime
- Night-time worst pain intensity score recorded in the morning upon awakening
- Sleep interference score (i.e., the subject's assessment of sleep interference due to pain) recorded in the morning upon awakening
- Neuropathic Pain Scale (NPS; pain quality questionnaire)
- Short-Form McGill Pain Questionnaire (SF-MPQ)
- Patient and clinician global impression of change
- Dynamic allodynia (response to a standardized light touch stimulus, a foam brush applied with light pressure to the site of maximum pain)
- Rescue analgesic use based on number of 500 mg acetaminophen tablets used
- Physical functioning derived from Brief Pain Inventory (BPI) questionnaire
- Quality of life measured on the Short Form-36 (SF-36) Form
- Emotional functioning measured on the Profile of Mood States (POMS) scale

Statistical Analysis Plan:

An analysis of covariance (ANCOVA) model, with terms for treatment, center, baseline pain, and body mass index (BMI), was used to analyze the primary efficacy outcome, the mean change in daily 24-hour average pain intensity scores from baseline to the end of treatment (randomized fixed dose, prior to down-titration). Each Horizant dose group (i.e., 1200, 2400, and 3600 mg/day) was compared to placebo, with a Dunnett's test used to adjust for multiple comparisons (i.e., maintain the overall alpha level at 0.05). The statistical reviewers felt that this approach is acceptable. The analyses were performed on the intent-to-treat (ITT) population defined as all randomized patients who received at least one dose of study treatment and who had at least one post-baseline assessment.

The applicant planned to use the last observation carried forward (LOCF) approach for imputation of missing data. At the pre-sNDA meeting, the Division expressed concern that good outcomes could be imputed for patients who discontinued due to adverse events (AEs) using this approach. The Applicant stated that results for the efficacy

analyses using a baseline observation carried forward (BOCF) approach would also be provided. In the actual NDA submission, the Applicant also provided analyses using a Hybrid approach (i.e., a combination of BOCF and LOCF). If a patient discontinued due to an AE, the Baseline value was imputed to any missing weeks on treatment. If a patient discontinued for any other reason, LOCF was used to replace missing values.

In addition to the analyses provided by the applicant, Ms. Meaker performed a continuous responder analysis, in which all patients who discontinue were classified as non-responders. The Van der Waerden Overall and Two-Sample Tests were used to compare differences in the distribution between placebo and each Horizant treatment.

Patient Demographics and Disposition: The patient population (n=376) for this study included the following demographic characteristics: predominantly Caucasian with a mean age of approximately 62 years, and BMI >30 kg/m^2 in approximately 40% of patients. Similar distributions by gender and age (≤ or > 65) were observed across treatment groups. Patient demographics are presented in Table 2. Overall, Ms. Meaker considered the treatment groups to be balanced across demographic and baseline characteristics.

A summary of patient disposition is depicted in Table 3. Ms. Meaker stated that the primary differences in patient disposition were the higher rate of dropouts due to lack of efficacy in the placebo groups, and AEs in the higher doses of Horizant groups.

Table 2: Demographics and Baseline Characteristics

	Placebo N=95	Horizant 1200 mg N=107	Horizant 2400 mg N=82	Horizant 3600 mg N=87	Total N=371
Age (y)					
Mean (SD)	61.7 (12.77)	61.7 (12.58)	64.1 (8.94)	61.3 (15.41)	62.1 (12.67)
Median	64.0	65.0	65.0	63.0	64.0
Range	18 – 83	18 – 87	21 – 83	20 – 92	18 – 92
Age Group, n (%)					
≤65 yrs	53 (56)	62 (58)	47 (57)	47 (54)	209 (56)
>65 yrs	42 (44)	45 (42)	35 (43)	40 (46)	162 (44)
Gender, n (%)					
Female	45 (47)	54 (50)	35 (43)	48 (55)	182 (49)
Male	50 (53)	53 (50)	47 (57)	39 (45)	189 (51)
Ethnicity, n (%)					
Hispanic/Latino	13 (14)	10 (9)	7 (9)	9 (10)	39 (11)
Not Hispanic/Latino	82 (86)	97 (91)	75 (91)	78 (90)	332 (89)
Race, n (%)					
White	79 (84)	94 (89)	69 (85)	73 (84)	315 (86)
African American/African	14 (15)	11 (10)	8 (10)	11 (13)	44 (12)
American Indian or Alaska	0	0	2 (2)	1 (1)	3 (<1)
Asian	1 (1)	1 (<1)	2 (2)	1 (1)	5 (1)
Japanese/East Asian Heritage/South East Asian Heritage	0	1 (<1)	1 (1)	1 (1)	3 (<1)
Central/South Asian Heritage	1 (1)	0	1 (1)	0	2 (<1)
Native Hawaiian or other	0	0	0	1 (1)	1 (<1)
BMI (kg/m^2), n (%)					
≤30	57 (60)	62 (58)	46 (57)	56 (64)	221 (60)
>30	38 (40)	45 (42)	35 (43)	31 (36)	149 (40)
Baseline 24-hour average					
4 - <6.5	56 (59)	63 (59)	58 (71)	47 (54)	224 (60)
6.5 - 10	39 (41)	44 (41)	24 (29)	40 (46)	147 (40)
Baseline 24-hour average pain					
Mean (SD)	6.33 (1.370)	6.28 (1.525)	5.98 (1.569)	6.47 (1.579)	NA
Range	4.1 – 9.4	4.0 – 10	4.0 – 9.8	4.0 – 10.0	NA

Source: Clinical Study Report, PXN110748, Table 1.11, Table 1.13, Table 2.1.
NA=Not applicable

Table 3: Patient Disposition

	Placebo	Horizant 1200mg	Horizant 2400mg	Horizant 3600mg
Randomized	95	107	84	90
Received Treatment = Intent-to-Treat (ITT)	95 (100%) 89 (94%)	107 (100%) 103 (96%)	82 (100%) 79 (96%)	87 (100%) 81 (93%)
Completed up-titration phase	65 (67%)	87 (79%)	61 (73%)	57 (64%)
Completed maintenance phase				
Reason for Discontinuation during Titration Phase:	6 (6%)	4 (4%)	5 (6%)	9 (10%)
Adverse event	4 (4%)	3 (3%)	3 (4%)	3 (3%)
Lack of efficacy	0	0	0	1 (1%)
Subject withdrew consent	0	1 (1%)	0	1 (1%)
Protocol Deviation	2 (2%)	0	1 (1%)	4 (5%)
Investigator discretion	0	0	1 (1%)	0
Reason for Discontinuation during Maintenance Phase:	24 (25%)	16 (15%)	18 (22%)	24 (28%)
Adverse event	7 (7%)	3 (3%)	9 (11%)	13 (15%)
Lack of efficacy	6 (6%)	1 (1%)	1 (1%)	3 (3%)
Subject withdrew consent	5 (5%)	5 (5%)	4 (5%)	3 (3%)
Protocol Deviation	3 (3%)	3 (3%)	3 (4%)	4 (4%)
Investigator discretion	2 (2%)	2 (2%)	1 (1%)	0
Lost to follow-up	1 (1%)	2 (2%)	0	1 (1%)
Discontinued after maintenance phase	1 (1%)	2 (2%)	1 (1%)	1 (1%)

Source: Katherine Meaker, MS, Statistical Review, Table 2, p. 7.

Results:

Primary Efficacy Analysis. The results for the primary efficacy endpoint are presented in Table 4. The Applicant demonstrated superiority over placebo for the 1200 mg/day Horizant dose using all three prespecified imputation approaches.

Table 4: Change from Baseline to Week 13 in Mean 24-hour Average Pain Intensity Score

	Placebo N=95	Horizant 1200 mg N=107	Horizant 2400 mg N=82	Horizant 3600 mg N=87
Baseline				
n	95	107	82	87
Mean (SD)	6.33 (1.370)	6.28 (1.525)	5.98 (1.569)	6.47 (1.579)
Change from Baseline to Week 13 (LOCF)				
n	95	106	80	87
Adjusted Mean (SE)[1]	-1.66 (0.216)	-2.47 (0.204)	-2.36 (0.237)	-2.72 (0.227)
Adjusted Mean Difference vs. Placebo[2]		-0.81	-0.70	-1.07
95% CI		(-1.40, -0.23)	(-1.33, -0.07)	(-1.68, -0.45)
p-value Adjusted for Multiplicity[3]		0.013	0.029	0.002
Unadjusted p-value[4]		0.007	0.029	0.001
Change from Baseline to Week 13 (BOCF)				
n	95	107	81	87
Adjusted Mean (SE)[1]	-1.32 (0.213)	-2.25 (0.200)	-1.97 (0.232)	-2.00 (0.223)
Adjusted Mean Difference vs. Placebo[2]		-0.94	-0.65	-0.68
95% CI		(-1.51, -0.36)	(-1.27, -0.03)	(-1.28, -0.08)
Unadjusted p-value[4]		0.001	0.040	0.027
Change from Baseline to Week 13 (Hybrid BOCF/LOCF)				
n	95	107	81	87
Adjusted Mean (SE)[1]	-1.59 (.220)	-2.33 (.207)	-2.10 (.240)	-2.24 (.231)
Adjusted Mean Difference vs. Placebo[2]		-0.74	-0.51	-0.65
95% CI		(-1.33,-0.15)	(-1.14, 0.13)	(-1.27, -0.03)
Unadjusted p-value[4]		0.014	0.119	0.040
Change from Baseline to Week 13 (Observed Cases)				
n	94	103	80	86
Adjusted Mean (SE)[1]	-1.64 (.218)	-2.50 (.208)	-2.36 (.238)	-2.72 (.228)
Adjusted Mean Difference vs. Placebo[2]		-0.86	-0.72	-1.08
95% CI		(-1.45, -0.27)	(-1.35, -0.09)	(-1.70, -0.47)
Unadjusted p-value[4]		0.004	0.025	0.001

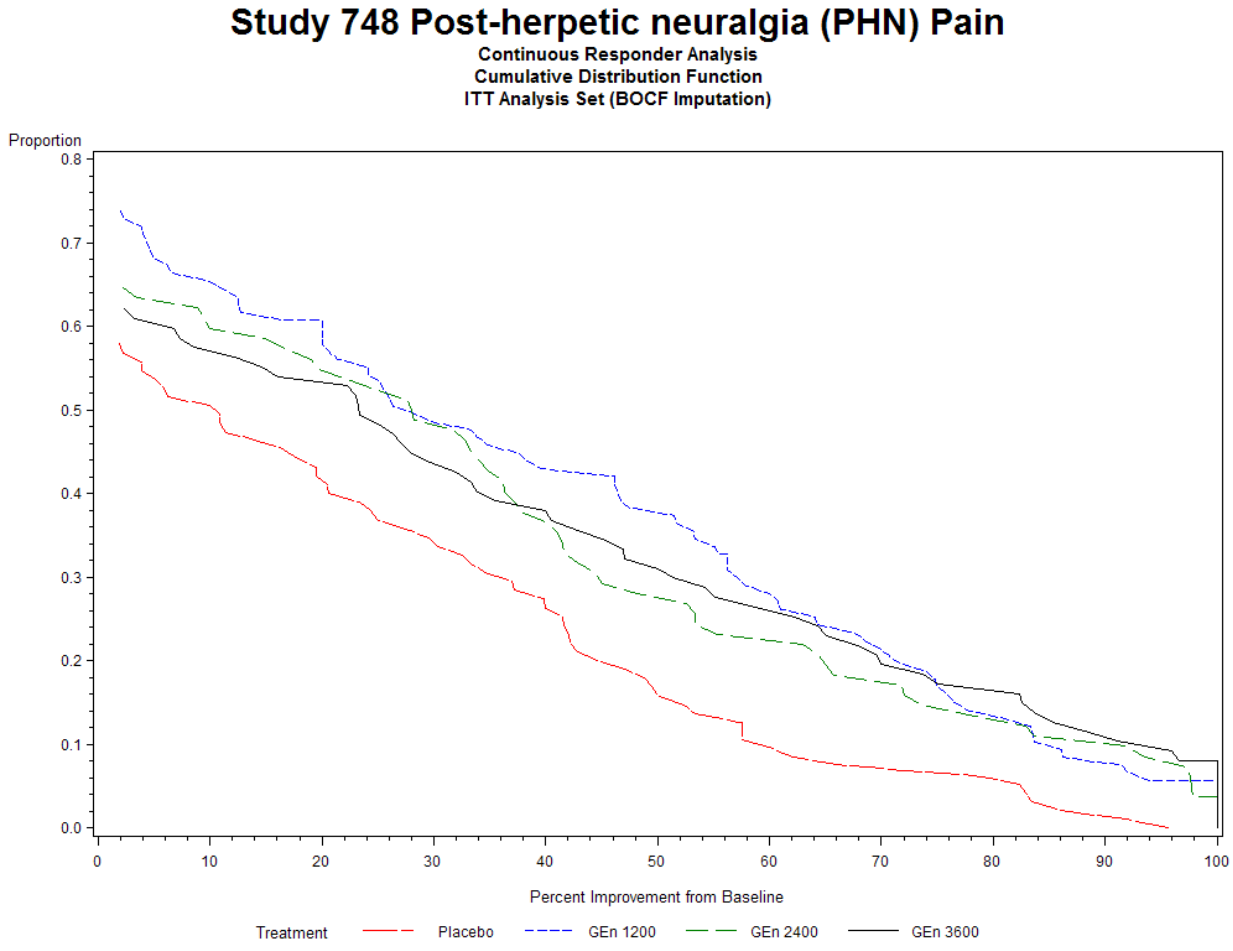
Source: Table 2.3, Table 2.9. Table 2.13, Table 2.17
Katherine Meaker, MS, Statistical Review, Table 4, p. 10.

1. The Adjusted Mean and SE are based on an ANCOVA model adjusted for BMI, baseline 24-hour average pain intensity and grouped center.
2. A negative treatment difference indicates benefit, relative to placebo.
3. Adjustments to p-values were made based on multiple treatment arms compared vs. placebo. A step-down procedure that uses Dunnett's test within a closed testing scheme for multiple comparisons with a common control was used to maintain the overall experiment-wise alpha level of 0.05 for the comparisons of Horizant vs. placebo.
4. Unadjusted p-values are provided for descriptive purposes, and were not adjusted for multiple comparisons.

Secondary Efficacy Analyses. Results for the continuous responder analysis were supportive of the primary efficacy analysis (Figure 2). Ms. Meaker reported that the distribution of the placebo group was statistically significantly different from those of the three Horizant groups (p-values: 0.016 overall test; <0.01 Placebo vs. Horizant 1200 mg/day; <0.04 placebo vs. Horizant 2400 mg/day; <0.04 placebo vs. Horizant 3600 mg/day).

Ms. Meaker also reanalyzed the mean daily dosage of rescue medication and the PGIC and concluded that the results of these analyses were consistent with Horizant 1200 mg/day being more efficacious than placebo.

Figure 2: Continuous Responder Analysis Curves (BOCF)



Source: Katherine Meaker, MS, Statistical Review, Figure 2, p. 13.

Interpretation/Conclusions:
The prespecified analyses demonstrated statistically significant differences between the proposed Horizant dose and placebo for the primary efficacy endpoint analyses. Ms. Meaker acknowledged that besides the imputation method planned to be used, there were no statistical issues, and the results are consistent and supportive as evidence for the efficacy of the Horizant 1200 mg/day dose for the PHN indication.

I concur with the efficacy findings and conclusions of the statistical reviewers.

SUPPORTING EFFICACY STUDIES
In addition to the Phase 2b efficacy study, the applicant submitted the following supporting data for efficacy and safety:

- Study PXN110527: A Phase 2a double-blind, 2-period (28 days each), crossover study of gabapentin enacarbil (i.e., 1200 mg/day vs. 3600 mg/day) in 138 PHN patients (96 randomized) who had a history of inadequate response to at least 1800 mg/day of gabapentin

  Results summarized in Dr. Levin's review:
  The primary endpoint, change from baseline in the mean 24-hour average pain intensity score for the last week of each treatment period, was according to the Applicant statistically significant (p=0.013) with an adjusted mean difference of -0.29 between the gabapentin enacarbil 3600 mg and gabapentin enacarbil 1200 mg treatments. The Applicant reports that the sensitivity analyses for the primary endpoint consistently had a treatment difference which was indicative of a benefit of gabapentin enacarbil 3600 mg relative to gabapentin enacarbil 1200 mg.

- Study XP009: A Phase 2a, randomized, double-blind, placebo-controlled, 2-week proof of concept study of gabapentin enacarbil (i.e., 1200 mg/day) vs. placebo in 115 PHN patients (102 randomized)

  Results summarized in Dr. Levin's review:
  The Applicant reported that the change from baseline in mean weekly pain score for the final week of treatment using LOCF data, gabapentin enacarbil 2400 mg demonstrated a statistically significant improvement over placebo with an adjusted mean treatment difference of -0.75 (p=0.032). The adjusted mean change from baseline for the gabapentin enacarbil treatment group was -2.02 while the placebo group reported an adjusted mean change from baseline of -1.27. The Applicant used the ITT population which contained only 47 subjects in the gabapentin enacarbil group, since one subject dropped out prior to receiving any dose of study medication.

- Two published reports describing efficacy studies conducted in the Neurontin registration program

1. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998; 280(21):1837-42.

   – A multicenter, randomized, double-blind, placebo-controlled, parallel design, 8-week study of gabapentin (4 week titration up to 3600 mg/day) in 229 PHN patients

2. Rice ASC, Maton S. Gabapentin in postherpetic neuralgia a randomized, double blind, placebo controlled study. Pain. 2001;94:215-24.

   – A multicenter, double-blind, randomized, placebo-controlled 7-week study of gabapentin (2400 mg) vs. placebo in 334 patients with PHN

Results summarized in Dr. Levin's review:
The efficacy findings from these two published randomized, double-blind, placebo-controlled studies, showed statistically significant improvement in pain compared to placebo. However, additional benefit of using doses greater than 1800 mg/day of gabapentin was not demonstrated.

Overall, results from the above four clinical trials were supportive. However, these data were not reviewed by the Office of Biostatistics. For further details refer to Dr. Levin's Clinical Review.

SUMMARY OF EFFICACY

The Applicant conducted a single adequate and well-controlled Phase 2b clinical trial, Study PXN110748, to support this sNDA submission. The design of this study (i.e., randomized, double-blind, placebo-controlled, parallel arm, multicenter) was adequate. Although three doses of Horizant (i.e., 1200, 2400, and 3600 mg/day) were studied, the Applicant is only seeking the approval of the 1200 mg/day dose based on the efficacy and safety data at this dose level.

The primary efficacy endpoint, change from baseline to Week 12 in the average 24-hour pain intensity score, and secondary endpoints (i.e., percent of subjects achieving various levels of reduction in average 24-hour pain intensity, the amount of rescue medication used, and patient global impression of change) for all three doses were compared to placebo. A Dunnett's test was used to adjust for multiplicity. .

The statistical reviewers reported that Horizant 1200 mg/day in this Phase 2b clinical trial was statistically superior to placebo for the primary and several supportive secondary endpoints, and that there is sufficient evidence to support the efficacy of Horizant 1200 mg/day for the management of PHN in adults. I concur with their conclusions that the data from this study provide sufficient evidence of effectiveness to support approval of Horizant for the proposed indication.

8. Safety

The review of clinical safety was conducted by Dr. Levin. In his review he evaluated the data supporting the safety and tolerability of Horizant in PHN.

The safety database for the Horizant clinical development program consists of exposure data on 2756 subjects exposed to at least one dose of Horizant. The Applicant's PHN clinical development program included 17 Phase 1 studies and three Phase 2 PHN studies. The Phase 1 studies were previously submitted and reviewed with the RLS NDA. In the Phase 2 PHN studies a total of 417 subjects were exposed to Horizant, as summarized in Table 5 below. In his review, Dr. Levin noted that due to differences in study populations, designs, and durations, there was no integration of data across the PHN studies.

Table 5: Summary of Phase 2 Studies in the PHN Clinical Developmental Program

Study	Phase	Design	Duration	Treatment	Exposure n (M/F)
PXN110748	2b	R, DB, PC, MD, PG Safety, Efficacy	12-wk	**Horizant** 1200 mg/d 2400 mg/d 3600 mg/d **Placebo**	276 (139/137) 107 (53/54) 82 (47/35) 87 (39/48) 95 (50/45)
XP009	2a	R, DB, PC, MD, PG Proof-of-Concept	2-wk	**Horizant** 1200 mg/d **Placebo**	47 (22/25) 54 (27/27)
PXN110527	2a	R, DB, 2-period CO	8-wk	**Horizant** 3600 mg/d **Horizant** 1200 ng/d	94 (57/36)*

*Gender by ITT Population (n=93), with 1 of 94 exposures without a post-baseline assessment.
Abbreviations: C, controlled; CO, crossover; DB, double-blind; F, female; M, male; MD, multiple-dose; PG, parallel group; R, randomized; wk, week.
Source: Derived in part from the Applicant's submission, Integrated Summary of Efficacy, Tables 10, 29, 42, and 58, p. 48, 75, and 89, respectively.

Common Adverse Events

The most common AEs reported with Horizant in Study PXN110748 were dizziness, somnolence and headache. The Applicant states that this is consistent with the RLS studies. Dizziness and somnolence were also the two most common dose-related treatment-emergent adverse events (TEAEs) observed in Study PXN110748, occurring in 15-30% and 8-40% of Horizant-treated subjects, respectively (see Table 6). Additionally, peripheral edema was reported in 6% to 7% of Horizant-treated subjects, with no events observed in the placebo arm. Other possible dose-related events included fatigue, insomnia and weight increased.

Table 6: Most Common Adverse Events (Incidence of at least 5% at Preferred Term Level in Any Horizant Group) in Study PXN110748

	Number (%) of Subjects				
	PBO (N=95)	GEn 1200 mg/day (N=107)	GEn 2400 mg/day (N=82)	GEn 3600 mg/day (N=87)	All GEn Doses (N=276)
Any Event	63 (66)	75 (70)	64 (78)	71 (82)	210 (76)
Preferred Term					
Dizziness	14 (15)	18 (17)	21 (26)	26 (30)	65 (24)
Somnolence	8 (8)	11 (10)	9 (11)	12 (14)	32 (12)
Headache	9 (9)	11 (10)	8 (10)	6 (7)	25 (9)
Nausea	5 (5)	9 (8)	3 (4)	8 (9)	20 (7)
Fatigue	1 (1)	5 (5)	4 (5)	9 (10)	18 (7)
Edema peripheral	0	6 (6)	6 (7)	5 (6)	17 (6)
Constipation	5 (5)	7 (7)	4 (5)	4 (5)	15 (5)
Diarrhea	5 (5)	6 (6)	2 (2)	6 (7)	14 (5)
Arthralgia	3 (3)	6 (6)	4 (5)	3 (3)	13 (5)
Insomnia	2 (2)	3 (3)	4 (5)	6 (7)	13 (5)
Nasopharyngitis	5 (5)	5 (5)	3 (4)	5 (6)	13 (5)
Urinary Tract Infection	3 (3)	8 (7)	2 (2)	1 (1)	11 (4)
Weight Increased	1 (1)	3 (3)	4 (5)	4 (5)	11 (4)
Back Pain	3 (3)	4 (4)	4 (5)	2 (2)	10 (4)
Dry Mouth	2 (2)	1 (<1)	4 (5)	4 (5)	9 (3)
Hypertension	1 (1)	2 (2)	4 (5)	2 (2)	8 (3)
Vision blurred	0	2 (2)	4 (5)	2 (2)	8 (3)
Nasal congestion	1 (1)	2 (2)	0	5 (6)	7 (3)
Flatulence	0	1 (<1)	1 (1)	4 (5)	6 (2)
Joint sprain	0	2 (2)	0	4 (5)	6 (2)
Tremor	0	0	0	4 (5)	4 (1)

Source: Summary Document Analysis Plan for Gabapentin Enacarbil PHN, Integrated Summary of Safety p. 33.

Deaths
There were a total of six deaths among 2756 subjects exposed to Horizant in the Applicant's clinical development program, but no deaths occurred among the 566 subjects in the Phase 2 PHN studies. The Applicant reported the cause of death for the six subjects as follows: 2 deaths (bronchopneumonia and accidental overdose), 2 deaths (asphyxia and fall), 1 death (lymphoma), and 1 death (completed suicide).

Serious Adverse Events (SAEs)
A total of 15 nonfatal SAEs were reported in 11 subjects from the PHN development program. Of these events, two subjects had received placebo, three occurred post-treatment in 3 subjects, and one was reported during both the treatment and post-treatment study phases. The breakdown of SAEs by the three PNH studies is as follows:

> *PXN110748.* Twelve SAEs were reported in nine subjects enrolled, of which one subject, allocated to the Horizant 1200 mg/day treatment arm, experienced an SAE of 'coronary artery disease' post-treatment. A summary of SAEs for this study is presented in Table 7.
>
> *PXN110527.* Two subjects experienced a total of three nonfatal SAEs (hallucination auditory, post-treatment depression, and post-treatment chest pain).
>
> XP009. No SAEs were reported during treatment or post-treatment.

Dr. Levin reviewed the narratives of all SAEs in the PHN development program, and concluded that there was no clear evidence that any of the SAEs were related to study drug. I concur with this assessment.

Table 7: Summary of Serious Adverse Events in Study PXN110748

System Organ Class Preferred Term	PXN110748			
	Placebo (N=95)	Horizant 1200 mg/d (n=107)	Horizant 2400 mg/d (N=82)	Horizant 3600 mg/d (N=87)
Number of subjects any event	2 (2%)	1 (1%)	4 (5%)	2 (2%)
Nervous System Disorders	0	0	2 (2%)	0
Intracranial aneurysm	0	0	1 (1%)	0
Multiple sclerosis	0	0	1 (1%)	0
Multiple sclerosis relapse	0	0	1 (1%)	0
Gastrointestinal disorders	0	0	0	1 (1%)
Gastritis	0	0	0	1 (1%)
General disorders and administration site conditions	0	0	1 (1%)	0
Chest pain (non cardiac)	0	0	1 (1%)	0
Infections and infestations	0	0	1 (1%)	0
Sinusitis	0	0	1 (1%)	0
Investigations	0	0	1 (1%)	0
Blood pressure increased	0	0	1 (1%)	0
Psychiatric disorders	0	0	1 (1%)	0
Anxiety	0	0	1 (1%)	0
Reproductive system and breast disorders	0	0	0	1 (1%)
Cystocele	0	0	0	1 (1%)
Cardiac disorders	1 (1%)	1 (1%)	0	0
Atrial fibrillation	1 (1%)	0	0	0
Coronary artery disease[1]		1 (1%)		
Injury, poisoning and procedural complications	1 (1%)	0	0	0
Vascular injury	1 (1%)	0	0	0

Source: Modified from Robert Levin, MD, Clinical Review, Table 25, p. 70.
[1]SAE occurred post-treatment: Subject hospitalized 9 days after last dose of Horizant for coronary artery disease and CABG

Discontinuations Due to TEAEs

The disposition of subjects in Study PXN110748 is presented in Table 3. Dropouts due to AEs appeared to be dose-related for the Horizant treatment arms (i.e., 1200, 2400 and 3600 mg/day at 6%, 15% and 18%, respectively). The Applicant noted that dropouts due to AEs were reported more often in the placebo arm (13%) than in the Horizant 1200 mg/day treatment group (6%).

Additional Safety Evaluations

Thorough QT Study (TQT). The Applicant's previously conducted TQT study (XP078) was inconclusive (i.e., the moxifloxacin control response failed to meet criteria for assay sensitivity). The Division of Neurology Products (DNP) requested that the TQT be repeated as a postmarketing requirement for the RLS indication. Since the mean changes in the QT interval observed in Study PXN110748 were not considered clinically meaningful across Horizant treatment groups, Dr. Levin felt that it is reasonable to conduct the TQT study as planned as a PMR for the RLS indication. I agree that this approach would be acceptable.

Carcinogenicity Studies. Previous carcinogenicity studies completed during the gabapentin and Horizant development programs reported a dose-related increase in the incidence of pancreatic acinar cell tumors in male Wistar rats. Drs. Emani and Levin noted that the safety margin for pancreatic acinar cell cancer at the proposed 1200 mg/day dose of Horizant is approximately 13 fold in humans, which is acceptable, especially since PHN is not considered a chronic condition. In the last RLS safety update, the Applicant noted that there have been six reports of carcinoma (1 on placebo, 1 misdiagnosis on Horizant, and 4 on Horizant).

Interchangeability of Gabapentin Products. Dr. Levin stated in his review that gabapentin products are not interchangeable, posing a potential safety concern if the same mg dose of Horizant and other gabapentin products are used interchangeably. This safety concern has been appropriately addressed in the Horizant label (Section 5.3, Lack of Interchangeability with Gabapentin).

Suicidal Behavior and Ideation. In his review, Dr. Levin notes that suicidality has been associated with antiepileptic drugs, including gabapentin. Although cases of suicidality were not reported in the PHN clinical development program, Horizant is a prodrug of gabapentin, and therefore may increase the risk for suicidality. This risk is appropriately addressed in the label.

Overdose, Drug Abuse Potential, Withdrawal and Rebound. CSS was consulted to review potential abuse liability issues of gabapentin that may relate to the Applicant's sNDA submission. For detailed information refer to the 21 March 2012 Memorandum provided by Stephen Sun, MD, CSS.

Although the Applicant was not able to identify any cases of overdose or abuse potential in their clinical development program, Dr. Levin noted that there have been infrequent AEs of 'feeling drunk', 'euphoric mood' and 'visual hallucination' that occurred only in Horizant treatment arms in the Phase 2b PHN efficacy study (Study PXN110748). Further, published articles and/or postmarketing reports include a few case reports of gabapentin withdrawal symptoms, abuse behaviors, and dependence from a withdrawal syndrome upon drug discontinuation. There was also a case of withdrawal seizure previously reported in the RLS clinical development program.

Dr. Sun reviewed postmarketing experience with gabapentin and Horizant from numerous sources. In his consult, he concluded that the rate of gabapentin misuse and abuse appears to be relatively low when considering the large denominator of prescriptions (i.e., more than (b) (4) in 2010) and doses administered when compared to other scheduled drugs of abuse. He made the following recommendations:

1. Continue surveillance of the misuse and abuse of these products (gabapentin, pregabalin, and gabapentin enacarbil) for two to five more years consistent with the Office of Surveillance and Epidemiology's recommendation.

2. The Label should reflect what is currently known on the abuse and dependence potential of gabapentin enacarbil. Such language should include the summary of postmarketing human experience with gabapentin.

I concur with these recommendations. CSS and the Division of Neurology Products (DNP) are revising Section 9 (i.e., Drug Abuse and Dependence) of the proposed Horizant label.

SUMMARY OF SAFETY

Dr. Levin concluded that the safety database of 2756 subjects exposed to at least one dose of Horizant in the Applicant's clinical development program, with 417 subjects exposed during the PHN development program, was adequate to assess safety of Horizant in the PHN patient population. A summary of major safety events for this sNDA included the following:

- ***Deaths:*** No deaths were reported in the PHN pain studies, but six deaths occurred overall. Dr. Levin felt that none of these deaths were clearly drug-related.

- ***SAEs:*** Eleven subjects out of 417 exposed reported a total of 15 nonfatal SAEs in the PHN pain studies. A causal association with Horizant could not be determined for any of these events.

- ***Discontinuations Due to TEAEs:*** Although dropouts due to AEs in the Phase 2b PHN efficacy study appeared to be dose-related, 6% and 13% of subjects discontinued study due to AEs in the Horizant 1200 mg/day and placebo treatment arms, respectively.

No new or unexpected safety signals were identified with the use of Horizant in the PHN patient population. Further, the safety profile of Horizant in these patients is similar to that observed with the use of gabapentin for PHN. Despite a two-fold higher Horizant dose, the safety profile in the PHN population is also consistent with that observed in the RLS clinical development program. Overall, Dr. Levin felt that the benefit to risk assessment for Horizant at the 1200 mg/day dose in the PHN patient population was acceptable for approval the Horizant for the management of PHN in adults.

I concur with Dr. Levin's assessment that there were no unusual or unexpected safety findings, and that the balance of potential risks to benefits associated with the use of Horizant in the management of PHN is acceptable.

9. Advisory Committee Meeting

No Advisory Committee was held for the sNDA.

10. Pediatrics

Horizant was designated by the Agency as an Orphan Drug for the treatment of PHN on 7 June 2011. Therefore, submission of a pediatric assessment, as required under the Pediatric Research Equity Act (PREA), does not apply to this application. Additionally, as noted by Dr. Levin in his review, the incidence of PHN is too low in the pediatric population to make pediatric studies practicable.

11. Other Relevant Regulatory Issues

Compliance with Good Clinical Practices
In his clinical review, Dr. Levin stated that the three Phase 2 PHN studies supporting this sNDA (i.e., PXN110748, PXN110527, and XP009) were conducted in accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

We requested that the Division of Good Clinical Practice Compliance (DGCPC)/Office of Scientific Investigations (OSI) inspect two clinical investigator sites for the Phase 2b efficacy study, PXN110748. These sites were chosen for inspection primarily based on their relatively high subject enrollment. At each site, subjects' records were audited to compare source documentation and electronic case report forms (eCRFs) to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, identification of AEs, and reporting of AEs in accordance with the protocol. Clinical laboratory report documentation, protocol deviation reports, concomitant medication usage, test article accountability, and IRB/IEC approvals and correspondence were also inspected. Results from the FDA inspections are presented in Table 8 below.

Table 8: Summary Review of Clinical Investigator Sites

Name of CI	Protocol # Site# Subject#	Inspection Date	Final Classification
Michael C. DeSantis, MD Clinical Trials of America, Inc 1730 N. Center Street Hickory, NC 28601	Protocol: PXN 110748 Site #051926 Enrolled: 14	January 3-5, 2012	VAI
Francois Blouin, MD Pro-Recherche Polyclinique des Ponts 1100 Boul. De La Rive-Sud, Bureau 120 Saint-Romuald, QC G6W 5M6 Canada	Protocol: PXN 110748 Site #048870 Enrolled: 20	February 13-17, 2012	Pending (Preliminary Classification VAI)

Source: Modified from Dr. Jean Mulinde's Clinical Inspection Summary Memorandum (9 March 2012).
Abbreviations: VAI, Voluntary Action Indicated (deviation(s) from the regulations).
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communications with the ORA field investigator; final inspection classification and final correspondence to the inspection entity has not issued.

Several general issues related to data flow were identified during inspection of the clinical investigators:

1. Source data for the individual pain intensity scores could not be verified at the clinical investigator sites because subjects entered their pain intensity scores into an electronic diary (eDiary) which was sent directly to a third party vendor (i.e., (b) (4)). While these data could be verified by inspection of the (b) (4) database that stored information transmitted from the individual subjects' eDairy entries, an inspection of (b) (4) was not requested as this entity had recently been inspected and no regulatory violations were identified in their conduct of other FDA regulated studies during that inspection. OSI agree that re-inspection of (b) (4) was not necessary at this time unless data issues were identified during the sNDA review.

2. Electronic case report forms (eCRF) were used by Clinical Investigators (CI) to record subject's data, which was then transmitted to the eCRF vendor (b) (4) and then in turn transmitted to the Sponsor. It is preferable that CI sites directly retain a copy of each subjects' eCRF in a write protected manner as source documentation, however, in this case CI's were provided with an archival CD that contained pdf versions of the subjects' eCRFs directly from the study Sponsor. When source data is returned to CI sites in this manner, the potential for manipulation of data exists. In this case there is no evidence of data manipulation based on comparison of additional hard copy source data at the CI sites to data points provided in NDA line listings. In addition, as data inconsistencies were not identified during the review, additional inspections of the Sponsor/Applicant and the eCRF vendor were not considered necessary.

At Site #051926, two subjects that should have been excluded from study participation due to screening CrCl values < 60 mL/min were enrolled. Both patients were randomized and received study medication. In his review, Dr. Levin stated that in total, 14 (4%) out of 376 subjects enrolled in Study PXN110748 were reported by the Applicant to have a CrCl of less than 60 mL/min, in violation of the protocol eligibility criteria. Since gabapentin is renally eliminated, enrollment of subjects with renal insufficiency could predispose patients to increased systemic exposure and the potential for AEs. The data submitted from this clinical investigator site were considered reliable and acceptable.

At Site #048870, a third subject with a low CrCl value was identified, but this subject did not receive study medication. A Form FDA 483 was issued to the clinical investigator for failure to ensure that the study was conducted in accordance with the investigational plan and protocol (i.e., enrollment of 1 subject that should have been excluded, and not dispensing study mediations kits according to schedule specified in the protocol). However, the data submitted from this clinical investigator site in support of the pending application were considered reliable and acceptable.

The Inspection Summary from Dr. Jean Mulinde, with concurrence from Dr. Susan Leibenhaut, indicates the following:

> *Based on the review of inspectional findings for clinical investigators Dr. DeSantis and Dr. Blouin, the data submitted by these sites for Study PXN110748 appear reliable in support of NDA 22399 S003. The final classification for the inspection of Dr. DeSantis is Voluntary Action Indicated (VAI) and the preliminary classification for the inspection of Dr. Blouin is also VAI, in each case, primarily for their failure to follow the investigational plan by enrollment of subjects that should have been excluded from the study due to the subjects' screening creatinine clearance values of < 60 mL/min.*

Dr. Levin stated that at this time there are no concerns regarding data integrity that would warrant further inspection by OSI. I concur with Dr. Levin and the recommendations provided by Drs. Mulinde and Leibenhaut. Based on their reviews, I feel that the data submitted to this sNDA are acceptable for use in support of the application.

Financial Disclosures

The Applicant submitted the Financial Certification and Disclosure document as required. In his clinical review, Dr. Levin noted that an investigator for the Phase 2b efficacy study (PXN110748) reported significant financial interest with the Applicant on the Financial Disclosure Form. This investigator enrolled (b) (4) of the 376 subjects enrolled in the study. Dr. Levin stated that inclusion of these (b) (4) study subjects (i.e., (b) (4) placebo, (b) (4) Horizant 1200 mg, and (b) (4) Horizant 3600 mg) is unlikely to affect the outcome of the study. I agree with this conclusion.

12. Labeling

The date of the last approved labeling for Horizant was on 13 December 2011. For the current submission, the Applicant originally proposed labeling that included updates and revisions primarily related to the PHN indication and the supporting information from their 12-week efficacy study. Sections that included relevant revisions are presented in Table 9 below.

Table 9: Proposed Labeling Changes

Labeling Section	Proposed Revisions
HIGHLIGHTS	(b) (4)
1 INDICATIONS AND USAGE (Sections 1.1 and 1.2)	
2 DOSAGE AND ADMINISTRATION (Sections 2.2 and 2.3)	
5 WARNINGS AND PRECAUTIONS (Sections 5.2 and 5.6)	
6 ADVERSE REACTIONS (Section 6.1)	
8 USE IN SPECIFIC POPULATIONS (Sections 8.1 and 8.5)	
9 DRUG ABUSE AND DEPENDENCE (Section 9.2)	
12 CLINICAL PHARMACOLOGY (Section 12.1)	
13 NONCLINICAL TOXICOLOGY (Section 13.1)	
14 CLINICAL STUDIES (Section 14.1)	
17 PATIENT COUNSELING INFORMATION (Section 17.6)	
MEDICATION GUIDE	

The Applicant also requested to include (b) (4) In the 3 May 2012 Clinical Pharmacology Review, it was recommended that Horizant not be administered to patients with End-Stage Renal Disease (ESRD) who require hemodialysis. This advice was also consistent with previous recommendations provided for the RLS NDA review. On 14 May 2012, in response to labeling changes by the Agency, the Applicant stated that they had inadvertently failed to distinguish between the RLS and PHN dosing recommendations for patients on

hemodialysis in their 16 January 2012 amendment, after the revision to the RLS dosing recommendation in hemodialysis was approved (December 2011). Their clarification and justification for why this information should be included in the label were as follows:

> *"As RLS symptoms occur predominantly in the evening/night, dosing of HORIZANT is recommended in the evening such that the maximal drug concentrations occur in the evening/night. Due to the lack of renal function to clear gabapentin, patients requiring dialysis have a sustained concentration day and night except during the dialysis session when the concentration declines rapidly. Patients with RLS need therapeutic concentration during the evening/night; therefore HORIZANT is not recommended for RLS patients with ESRD receiving hemodialysis. However, patients with PHN need sustained therapeutic concentration day and night. The profile of concentrations with twice daily dosing in the treatment of PHN support reduced dosing in patients with PHN and on hemodialysis."*

On 17 May 2012, an addendum was submitted to the Clinical Pharmacology Review. In this addendum, it was acknowledged that PHN patients may need to maintain therapeutic serum concentrations throughout the day. Further, based on simulations provided by the Applicant, the proposed 300 mg dose following every dialysis would allow ESRD patients with renal clearance of ≤ 1% to achieve serum concentrations comparable to those observed in patients without significant renal impairment (i.e., CrCl 60-120 mL/min). Therefore, the Applicant's proposed dosing recommendations for hemodialysis patients with a CrCl < 15 mL/min (i.e., 300 mg following every dialysis and increase to 600 mg if necessary) is acceptable to the Clinical Pharmacology Review Team.

Samuel Skariah, PharmD, DPDP and L. Shenee Toombs, PharmD, DCDP, submitted a Label and Labeling Review (4 May 2012) that evaluated the Horizant package insert (PI) and Medication Guide (MG) for vulnerability that could lead to medication errors. They also assessed the readability, clarity and consistency of labeling throughout the package insert and Medication Guide and across labeling between other gabapentin products.

Sharon Mills, BSN, DMPP, provided a Patient Labeling Review (23 April 2012) in response to the Division's request to review the Applicant's proposed MG. DMPP simplified wording and clarified concepts, ensured the consistency between the MG, PI and approved comparator labeling, removed unnecessary or redundant information, and ensured that the MG meets the criteria specified in the regulations and FDA Guidance for Useful Written Consumer Medication Information.

The final stages of the labeling review within the Division are still ongoing. CSS and DNP are currently reviewing Section 9 (Drug Abuse and Dependence) for additional labeling changes to be conveyed to the Applicant. The preliminary draft labeling provided by DNP for Sections 9.1, 9.2, and 9.3 of the proposed Horizant label is as follows:

9.1 Controlled Substance

[Drug name] is not a scheduled drug.

9.2 Abuse

Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta or kappa), or cannabinoid 1 receptor sites. A small number of postmarketing cases report gabapentin misuse and abuse. These individuals were taking higher than recommended doses of gabapentin for unapproved uses. Most of the individuals described in these reports had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances. When prescribing [*insert drug name*] carefully evaluate patients for a history of drug abuse and observe them for signs and symptoms of gabapentin misuse or abuse (e.g., development of tolerance, self-dose escalation, and drug-seeking behavior).

9.3 Dependence

There are rare postmarketing reports of individuals experiencing withdrawal symptoms shortly after discontinuing higher than recommended doses of gabapentin used to treat illnesses for which the drug is not approved. Such symptoms included agitation, disorientation and confusion after suddenly discontinuing gabapentin that resolved after restarting gabapentin. Most of these individuals had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances. The dependence and abuse potential of [*insert drug name*] has not been evaluated in human studies.

13. Recommendations/Risk-Benefit Assessment

RECOMMENDED REGULATORY ACTION

Approval

RISK-BENEFIT ASSESSMENT

No new or unexpected safety signals were identified by Dr. Levin in his review of the data submitted for this sNDA. In general, the safety profile of Horizant in patients with PHN is similar to what was observed with the use of gabapentin in this patient population. Additionally, despite Horizant doses approximately twice as high as those used to treat RLS, the safety profiles of these two doses appear to be comparable.

The Statistical and Clinical reviewers for this sNDA felt that the single adequate and well-controlled clinical trial and supporting information submitted by the Applicant provided sufficient evidence of effectiveness for the use of Horizant for the proposed dose and indication. Since there was no clear evidence for improved efficacy with doses of Horizant greater than 1200 mg/day, and the incidence of adverse reactions may increase with higher doses, Dr. Levin recommended approval of only the 1200 mg/day dose.

I concur with the Clinical and Statistical assessments of the safety and efficacy findings from the clinical trial data submitted for this application. Further, considering the well known chemical and pharmacologic characteristics of the approved listed drug, Neurontin (gabapentin), and its established efficacy and safety, I feel that the benefits of Horizant outweigh potential risks for the proposed indication: management of postherpetic neuralgia (PHN) in adults.

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/s/

FRANK PUCINO
05/19/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-399/S-003

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22399
Priority or Standard	Standard
Submit Date(s)	09 August 2011
Received Date(s)	09 August 2011
PDUFA Goal Date	09 June 2012
Division / Office	Division of Anesthesia, Analgesia, and Addiction Products/ODE II
Reviewer Name(s)	Robert A. Levin, M.D.
Review Completion Date	03 May 2012
Established Name	Gabapentin Enacarbil Extended-Release Tablets
(Proposed) Trade Name	Horizant
Therapeutic Class	Antiepileptic
Applicant	GlaxoSmithKline
Formulation(s)	600 mg Tablet
Dosing Regimen	Start with 600 mg in the morning, then increase to 600 mg twice daily starting on day four
Indication(s)	Postherpetic Neuralgia (PHN)
Intended Population(s)	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend an Approval action for the subject of the current application, Horizant (gabapentin enacarbil) Extended-Release Tablets for the indication for the management of postherpetic neuralgia (PHN) in adults.

Review of the clinical data reveals evidence of efficacy of gabapentin enacarbil (GEn), a prodrug of gabapentin, in PHN in the adult population. The basis for determining clinical efficacy is one principal clinical trial of 12 weeks duration using the primary endpoint of change in pain from baseline to week 12. Two Phase 2 studies are supportive of the finding of efficacy in the principal study. Additionally, efficacy of the parent drug, gabapentin, in the treatment of PHN has been demonstrated in two studies (Rowbotham,1998; Rice, 2001) submitted by the Applicant in support of this 505(b)(2) application.

The safety profile of GEn is similar to that of gabapentin. For a summary of potential safety issues the reader is referred to Section 1.2.

1.2 Risk Benefit Assessment

Benefit
Efficacy for this 505(b)(2) application was demonstrated in one adequate and well-controlled (i.e., randomized, double-blind, placebo-controlled) study (PXN110748). There was statistically significantly less pain at 12 weeks in subjects with neuropathic pain associated with post-herpetic neuralgia. Efficacy was also supported by secondary endpoints including rescue medication use, patient global impression of change and cumulative responder analysis. Efficacy of GEn was demonstrated in the principal study with all doses studied from 1200 mg to 3600 mg/day with comparable effects across the dose range. No additional benefit of using doses greater than 1200 mg/day was demonstrated.

The Applicant submitted two Phase 2 studies: Study PXN110527 a double-blind, 2-period (each period 28 days), crossover study of two doses of GEn (1200 mg/day and 3600 mg/day) in PHN subjects who had a history of inadequate response to at least 1800 mg/day of gabapentin and Study XP009 a randomized, double-blind, placebo-controlled, 2-week proof of concept study in PHN comparing GEn 2400 mg/day to placebo. The decision for approving this product was not based on efficacy findings from these two studies since they were not appropriately designed to demonstrate efficacy (i.e., duration of two weeks or no placebo control). Therefore the efficacy findings from these studies were not reviewed by the FDA statistician. However, the

efficacy findings were supportive of the findings in Study PXN110748. For study PXN110527, the Applicant reported that the primary endpoint, change from baseline in the mean 24-hour average pain intensity score for the last week of each treatment period, was statistically significant. For Study XP009, the primary endpoint of change from baseline in mean weekly pain score for the final week of treatment was reported as showing statistically significant improvement for GEn 2400 mg over placebo.

The Applicant submitted published results from the two principal studies used to demonstrate efficacy in the Neurontin registration program for the indication of the treatment of PHN. Both randomized, double-blind, placebo-controlled studies showed significant differences in efficacy from placebo. However, additional benefit of doses greater than 1800 mg/day of gabapentin was not demonstrated. The Neurontin label states that efficacy was demonstrated over a range of doses from 1800 mg/day to 3600 mg/day with comparable effects across the dose range.

Summary of Benefit
The Applicant has demonstrated efficacy for GEn for the treatment of PHN with all doses studied from 1200 mg to 3600 mg/day with comparable effects across the dose range. The evidence of efficacy is supported by two additional Phase 2 studies and two published reports in the literature submitted by the Applicant.

Risk
The GEn development program provided adequate exposure to assess safety with a total of 2756 subjects exposed to at least one dose of GEn regardless of phase or indication and a total of 417 subjects exposed to GEn in Phase 2 PHN studies. There were no deaths in the post-herpetic pain studies but six deaths occurred overall. No death appeared to be clearly drug-related. Although, a contributory role by GEn could not be completely excluded in one patient that committed suicide, since suicide is a labeled event in subjects on antiepiletics, this subject also had other risks for suicide.

Potential serious or unique safety issues for GEn are summarized below. These safety issues are not considered serious enough to prevent approval of GEn and/or appropriate mitigation measures exist to minimize the risk to an acceptable level.

Thorough QT Study
The Applicant previously conducted a thorough QT (TQT) study at 6000 mg of GEn. The Interdisciplinary Review Team (IRT) for TQT studies found the study to be inconclusive since the moxifloxacin response failed to meet criteria for assay sensitivity. The Division of Neurology Products requested that an additional TQT study be conducted as a postmarketing requirement for the RLS indication. The Division of Anesthesia, Analgesia, and Addiction Products in the Pre-NDA meeting for PHN indicated that the results of the TQT study submitted in RLS NDA 022399 may be used to support the filing of the PHN sNDA but whether the QT study provides sufficient information to proceed with approval of the PHN sNDA will depend on the totality of the

data. The ECG data collected in the principal efficacy study, PXN110748, does not demonstrate any clinically significant effect of GEn on QT interval. Therefore, it is reasonable to conduct the TQT study as already planned as a postmarketing requirement for the RLS indication.

Preclinical Pancreatic Acinar Cell Carcinoma

Carcinogenicity studies completed during the development programs for gabapentin (Neurontin) and GEn, reported a dose related increase in the incidence of pancreatic acinar cell tumors in Wistar rats. The relevance of this finding to humans is uncertain. For GEn 600 mg/day approved for RLS indication, the safety margin for pancreatic acinar cell cancer in humans is 25 fold. The safety margin for pancreatic acinar cell cancer for GEn 1200 mg/day, the proposed dose for PHN, is (b) (4) fold in humans. This safety margin is considered adequate and furthermore, additional safety exists since PHN is not considered a chronic condition.

Lack of Interchangeability with Gabapentin

GEn is not interchangeable with other gabapentin products since the same dose of GEn and gabapentin results in different plasma concentrations of gabapentin. This safety concern can be appropriately addressed in the label.

Suicidal Behavior and Ideation

Antiepileptic drugs including gabapentin have been associated with an increased risk for suicidality. Because GEn is a prodrug of gabapentin, it is reasonable to conclude that GEn may also increase the risk of suicidal thoughts or behavior. This increased risk is appropriately addressed in the label with the existing language on antiepileptic drugs and suicidal behavior and ideation. Review of the PHN studies revealed no clear evidence that GEn increases the risk of suicide.

Discussion of Risks

The risks associated with GEn are well known and appropriate mitigation measures can be made in the label. The safety margin of 13 fold for the nonclinical finding of pancreatic acinar tumor is considered adequate especially since PHN is not considered a chronic indication.

Risk Benefit Analysis

Since there is no clear evidence of improved efficacy with doses of GEn greater than 1200 mg/day but there is an increased incidence of adverse events with these doses, recommendation is made for approval of only the 1200 mg/day dose. There is a positive benefit to risk assessment for GEn 1200 mg/day for the treatment of PHN.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A risk evaluation and mitigation strategies (REMS) program will not be necessary. However, the Division of Neurology Products, in agreement with the Office of Surveillance and Epidemiology determined during the NDA review for RLS that a Medication Guide would be required although it should not be part of a REMS. I concur with the prior recommendations made by the Division of Neurology Products that a REMS program will not be necessary, although a Medication Guide will still be required.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant will not be required to conduct pediatric studies to fulfill the requirements of the Pediatric Research Equity Act since GEn was granted orphan-drug status for "management of postherpetic neuralgia in adults" and furthermore the incidence of PHN is too low in the pediatric population to make pediatric studies feasible.

2 Introduction and Regulatory Background

2.1 Product Information

Gabapentin enacarbil (GEn) is an extended release prodrug of gabapentin, a drug marketed (tradename Neurontin) for the treatment of patients with epilepsy, and for the treatment of patients with postherpetic neuralgia. Horizant (GEn) was approved as an oral formulation (NDA 22399) on April 6, 2011 for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS). GEn compared to gabapentin is more readily and completely absorbed from the gastrointestinal tract.

Trade Name (established name): Horizant (gabapentin enacarbil) Extended-Release Tablets

Indication
Approved Indications
Horizant Extended-Release Tablets are indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome in adults.

Proposed Indication
Horizant Extended-Release Tablets are indicated for the management of postherpetic neuralgia (PHN) in adults.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are five drugs approved for the treatment of neuropathic pain associated with postherpetic neuralgia (Table 1). Unapproved treatment options for PHN include antidepressants and for severe pain opioid analgesics and intrathecal glucocorticoids have been used.

Table 1: Drugs Approved for Management of Postherpetic Neuralgia

Drugs Approved for Management of Postherpetic Neuralgia				
Generic Name	**Brand Name**	**Manufacturer**	**Generic Available**	**Dosage Form**
Gabapentin	Neurontin	Pfizer	Yes	Tablets and Oral Solution
Gabapentin (extended-release)	Gralise	Depomed	No	Tablets
Pregabalin	Lyrica	Pfizer	No	Capsules and Oral Solution
Capsaicin 8%	Qutenza	Neurogesx	No	Topical Patch
Lidocaine 5%	Lidoderm	Endo Pharmaceuticals	No	Topical Patch

2.3 Availability of Proposed Active Ingredient in the United States

GEn (Horizant) is a prodrug of gabapentin, a drug marketed under the tradename Neurontin. Horizant was approved as an oral formulation (NDA 22399) on April 6, 2011 for the treatment of moderate-to-severe primary RLS. Neurontin was first approved in the United States in December 1993 as an add-on medication for treatment of refractory partial epilepsy. In May 2004, Neurontin was approved for postherpetic neuralgia. There are several generic gabapentin products approved in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

Antiepileptic drugs, including gabapentin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Because GEn is a prodrug of gabapentin, it is reasonable to conclude that GEn may also increase the risk of suicidal thoughts or behavior. The currently approved label for Horizant includes the standard warning that patients treated with any antiepileptic for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior,

and/or any unusual changes in mood or behavior. This warning appears to adequately address the risk of suicidal behavior and ideation.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2 displays highlights of the regulatory activity that occurred during the clinical development program for Horizant.

Table 2: Regulatory Interactions between the FDA and the Applicant

Regulatory Interactions between the FDA and the Applicant	
Date	**Topics**
October 1, 2003 IND 068341 opened	• Development program for XP13512 (now referred to as gabapentin enacarbril [GEn]) for PHN initiated under this IND by XenoPort
December 13, 2004 IND 071352 filed with DNP	• Development program for XP13512 conducted under this IND for indication of RLS
April 20, 2007 (b) (4)	• (b) (4)
February 17, 2010 Complete Response for GEn for treatment of RLS issued by DNP	• Primary reason for CR action was that the NDA did not adequately address the preclinical finding of pancreatic acinar cell carcinoma observed in carcinogenicity studies for both GEn and Neurontin (safety margin approximately 8 fold for GEn 600 mg/day).
October 6, 2010 NDA resubmitted for RLS	• Applicant's resubmission included new preclinical data and rationale for greater safety margin for pancreatic acinar cell carcinoma. DNP determined that the safety margin is about 25 for GEn 600 mg/day.
March 17, 2011 Pre-NDA Meeting with DAAAP for PHN	The Division made the following comments to the Applicant during the Pre-NDA meeting: • A supplemental NDA submission is acceptable, provided that at the time of submission the product is approved for RLS in the Division of Neurology Products • A 505(b)(2) submission is acceptable but the degree to which GSK can rely on information that it does not have a right of reference to will be a review issue • The incidence of PHN is too low in the pediatric population to make pediatric studies feasible • The nonclinical information appears sufficient to support submission of an NDA for 1200 mg/day but whether this data supports approval will be a review issue • We are unable to agree that the risk of carcinogenicity at

Regulatory Interactions between the FDA and the Applicant	
	the proposed 1200 mg/day dose has been adequately addressed until we review the data. • The pharmacokinetic (PK) exposure comparison between Horizant and Neurontin seems reasonable. However, you did not conduct a direct relative BA/BE study to compare the bioavailability of gabapentin between GEn at 600 mg BID and the reference product Neurontin 600 mg TID. Whether or not the comparison based on extrapolation would be adequate will be a review issue. • No additional drug-drug interaction studies will be needed for filing. • The TQT study submitted in the RLS NDA may be used to support the filing of the PHN sNDA. However, whether the QT study provides sufficient information for approval of the PHN sNDA will depend on the totality of the data. o The DNP requested that an additional TQT study be conducted as a postmarketing requirement for RLS indication because the control moxifloxacin group did not have the expected change. • Provided that the data submitted to the PHN sNDA do not suggest significant CNS depression, the potential effects on driving and operating heavy machinery can be addressed in labeling. o In support of the RLS NDA, a simulated driving study (XP083) was conducted in subjects with RLS on GEn 1200 or 1800 mg once daily. The 1800 mg dose exceeded the proposed 1200 mg/day (600 mg BID) dose of GEn for the treatment of PHN. • Normally, you would need two adequate and well-controlled studies for a new chemical entity; as a 505 (b)(2) application for a prodrug, you might be able to reference the studies from your listed drug relied upon for approval, gabapentin, which would result in your only needing one additional study. However, that would require that you demonstrate that most of the active drug in the systemic circulation was gabapentin and not the prodrug. • Provide the pooled datasets for all safety data from the double-blind, placebo-controlled studies in PHN; however, do not pool safety data for Study PXN110527 (no placebo control) with any other study. • Your proposal that safety data from non-PHN studies should not be integrated with PHN studies data in the

Regulatory Interactions between the FDA and the Applicant	
	analyses in the ISS appears reasonable.
April 6, 2011 Approval for RLS	Approved for the treatment of moderate-to-severe primary RLS. The Approval Letter contained the following required pediatric assessments and postmarketing requirements: • Pediatric PK/PD, efficacy and safety and long-term safety studies in adolescents with RLS • A driving study in adolescent patients with RLS using diphenhydramine as active control • An *in vitro* study to evaluate the potential for GEn and gabapentin to be inhibitors of CYP2C8 and CYP2B6 • An *in vitro* dissolution study to evaluate alcohol dose dumping using the final dissolution method, and evaluate different concentrations of alcohol up to 40% (0, 5, 10, 20, and 40%) • A simulated driving trial in healthy adult subjects treated with 600 mg GEn that includes active comparator and placebo arms • A simulated driving trial in healthy adult subjects treated with an appropriate dose of GEn (determined in PMC efficacy study of lowest effective dose) that includes active comparator and placebo arms • An adequate, randomized, double-blind, placebo- and moxifloxacin-controlled trial to evaluate the effect of GEn on cardiac repolarization in healthy adult subjects • A clinical drug-drug interaction trial to evaluate the pharmacokinetic and the pharmacodynamic interaction between GEn and morphine. The Approval Letter contained the following postmarketing commitments: • Develop a dosage form that will allow for a 300 mg dose that could be taken once daily in patients with severe renal impairment, including patients on hemodialysis • Conduct a randomized, placebo-controlled, double-blind, parallel-group clinical trial of GEn at 300 mg/day, 450 mg/day and 600 mg/day in patients with moderate to severe symptoms of RLS
June 7, 2011 Orphan-drug status granted	• GEn was granted orphan-drug designation in the US (Orphan Drug Designation Request #10-3307) for the management of PHN on 07 June 2011
August 9, 2011 NDA submitted for PHN	• NDA for PHN submitted to DAAAP

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA was submitted in Electronic Common Technical Document (eCTD) format. All sections/modules were completed appropriately. The submission was reasonably well-organized and paginated to allow for an acceptable review.

3.2 Compliance with Good Clinical Practices

Principal efficacy Study PXN110748 and supportive studies PXN110527 and XP009 were conducted in accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. Prior to initiating the study, each subject gave informed consent before any study-specific procedures were performed.

The Division of Scientific Investigation (DSI) inspected two sites for Study PXN110748. The clinical investigator sites chosen for inspection, Site #048870 (Francois Blouin, MD) and Site #051926 (Michael C. DeSantis, MD) were amongst the highest enrolling domestic and foreign centers.

Overall, the data submitted by the two inspected sites were considered reliable and acceptable for use in support of the NDA. However, failure to follow the protocol exclusion criteria was identified for two subjects at site #051926 and one subject at site #048870. At site #051926 two subjects that should have been excluded from the protocol based on screening creatinine clearance (CrCl) values less than 60 mL/min were not excluded. Subject #7753 (randomized to 1200 mg group) with a screening CrCl=52 mL/min, and Subject #7755 (randomized to placebo group) with a screening CrCl=39 mL/min were randomized and received study therapy. Randomization of these subjects in error was reported to the Applicant as protocol deviations, but not until approximately one year after randomization and treatment had occurred. Subject #7753 withdrew from the study on Day 8 with complaints of intolerable fatigue and numbness. One subject enrolled at site #051926 that should have been excluded due to having a CrCl<60 mL/min was removed from the study prior to receipt of any study drug.

Reviewer's Note: A total of 14 subjects were reported by the Applicant in the NDA submission as enrolled with CrCl less than 60 mL/min, in violation of the protocol eligibility criteria.

DSI noted two other general issues concerning the conduct of the study. First DSI was not able to confirm the individual pain scores subjects entered. Subjects entered their pain scores directly into an eDairy and this data went directly to a 3rd party vendor (b) (4) The clinical investigators did not view all individual pain scores entered but were able to view average pain scores to make determination of whether subjects were eligible for randomization. They appeared to have recorded this data on paper source documents. Because the study was set up this way, DSI was not able to confirm the individual pain scores during their inspections. DSI could confirm the pain scores if they looked at the (b) (4) database that stored information transmitted from the individual subjects' eDairy entry. However DSI recently inspected (b) (4) for another application and found no problems with their procedures of handling of data in that case. DSI did not feel that re-inspection of (b) (4) was necessary unless irregularities or inconsistencies in data were identified during the review.

The second issue was a general one of appropriateness of data flow. Data for this study was collected via electronic CRFs and then transmitted to the Applicant. The clinical investigator (CI) did not retain a write protected copy of the eCRF that they signed-off on but appeared to have received these CDs directly from GSK. These CDs, part of the source documentation at the CI sites, have then traveled through the Applicant which raises questions of whether data might have been manipulated. DSI did not identify any issues during the inspections that suggest that GSK in any way manipulated the data. DSI suggested that if during the NDA review any data inconsistencies raise concern then an inspection of the Applicant and electronic data capture vendor can be compared. At this time there are no concerns regarding data integrity that would warrant further inspection by DSI.

DSI concluded that not withstanding the observations noted above the data provided by Dr. DeSantis's site and Dr. Blouin's site for Study PXN110748 that were submitted to the Agency in support of NDA 22399 S003 appear to be reliable and acceptable for use in support to the pending application.

3.3 Financial Disclosures

GlaxoSmithKline has adequately disclosed financial arrangements with clinical investigators. The Applicant has submitted Debarment Certification and FDA Form 3454 certifying that the clinical investigators who supervised Studies PXN110527, PXN110748 and PXN111044 (XP009) in support of this application:

- Did not participate in any financial arrangement with the Applicant, whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study [as defined in 21 CFR 54.2(a)]:
- Had no proprietary interest in this product or significant equity interest in the Applicant [as defined in 21 CFR 54.2(b)]: and

- Was not the recipient of significant payments of other sorts [as defined in 21 CFR 54.2(f)]

At one site (b) (4) in Study PXN110748, an investigator reported significant financial interest in GSK on the Financial Disclosure Form. The (b) (4) subjects ((b) placebo, (b) (4) GEn 1200 mg and (b) (4) GEn 3600 mg) out of a total of 376 subjects (b) (4) enrolled at this site is unlikely to affect the outcome of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There was no new CMC data included in this submission related to the product under review. The Applicant did conduct study (b) (4) GSK is (b) (4).

4.2 Clinical Microbiology

GEn is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

4.3 Preclinical Pharmacology/Toxicology

The following information was obtained from the Pharmacology/Toxicology Memorandum by FDA pharmacologist, Dr. Armaghan Emami. She concluded that since the existing nonclinical development program submitted to the RLS NDA contains a nonclinical safety assessment of oral administration of GEn at a daily dose of up to 1200 mg that no additional nonclinical studies are considered necessary to support the current application.

Dr. Emami noted that in the previous review of the NDA for RLS, there was a concern about pancreatic tumors observed in the rat. She provides the following explanation for calculating the safety margin for pancreatic tumors for the proposed GEn 1200 mg dose.

> … the Applicant has referred to the Agency's finding of safety for gabapentin (Neurontin). Carcinogenicity studies with gabapentin showed the same tumor finding in rats, although only in males. The Agency considered 1000 mg/kg to be the no-effect dose for the occurrence of carcinoma. The Applicant provided new data assessing the plasma exposure to gabapentin under conditions similar to those used in the original gabapentin rat carcinogenicity study in order to bridge to the exposures observed in the GEn study. The exposure to gabapentin in the rat at 1000 mg gabapentin/kg was

> approximately 13 times higher than the human exposure and was intermediate between the exposures observed at 500 and 2000 mg/kg GEn (Note: Increases in the incidence of pancreatic acinar adenoma and carcinoma were found in 2000 mg/kg males but not at 500 mg/kg). Therefore, the NOAEL for the pancreatic tumors in rats actually occurs at an exposure to gabapentin that is 13-fold higher than the clinical exposure.

Dr. Emami further notes that the potential carcinogenic risk of the proposed drug product is likely reduced given that PHN is not a chronic disorder that requires long-treatment (i.e., > 3 months).

Overall, Dr. Emami concluded that from the nonclinical pharmacology toxicology perspective, this NDA may be approved.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

GEn is a prodrug of gabapentin and, accordingly, its therapeutic effects in PHN are attributable to gabapentin. The mechanism of action by which gabapentin is efficacious in PHN is unknown, but in animal models of analgesia, gabapentin prevents allodynia and hyperalgesia.

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. *In vitro* studies have shown that gabapentin binds with high affinity to the $\alpha 2\delta$ subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of GEn in PHN is unknown.

4.4.2 Pharmacodynamics

There were no apparent clinically significant cardiovascular effects of GEn (i.e., hypotension or QT prolongation). However, the TQT study was considered to be inadequate by the IRT and will be repeated as a RLS Postmarketing Requirements.

4.4.3 Pharmacokinetics

GEn is an extended-release formulation of a prodrug of gabapentin. GEn provides approximately dose-proportional and extended exposure to gabapentin over the range 300 to 6,000 mg. GEn and gabapentin are not interchangeable because the same daily dose of each results in different plasma concentrations of gabapentin.

Absorption
The pathway for absorption of GEn is believed to include active transport via a proton-linked monocarboxylate transporter, MCT-1. This transporter is expressed at high levels

in the intestinal tract and is not saturated by administration of high doses of GEn. Mean bioavailability of gabapentin (based on urinary recovery of gabapentin) for GEn in the fed state is about 75%. Bioavailability under fasting conditions has been estimated by gabapentin urinary recovery to be 42% to 65%. In a food effect study, the exposure of gabapentin increased by 24%, 34%, and 44% with low, moderate, and high fat meals, respectively. The Tmax of gabapentin after administration of 600 mg of GEn was 5.0 hours in fasted subjects and 7.3 hours in fed subjects. Steady state is reached in 2 days with daily administration.

Distribution
Plasma protein binding of gabapentin has been reported to be <3%. The apparent volume of distribution of gabapentin in subjects receiving GEn is 76 L.

Metabolism
After oral administration, GEn undergoes extensive first-pass hydrolysis by non-specific carboxylesterases primarily in enterocytes and to a lesser extent in the liver, to form gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid. Levels of GEn in blood are low and transient (≤2% of corresponding gabapentin plasma levels). Released gabapentin is not appreciably metabolized in humans. Neither GEn nor gabapentin are substrates, inhibitors, or inducers of the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). It is not known if GEn is an inhibitor of CYP2B6 and CYP2C8. GEn is neither a substrate nor an inhibitor of P-glycoprotein *in vitro*.

Elimination
Following hydrolysis of GEn, the released gabapentin is excreted unchanged by the kidney. Gabapentin renal excretion is believed to involve a component of active secretion via an organic cation transporter (OCT2) present in the kidney. In a human pharmacokinetic study with immediate release 14C GEn, mean recovery of total radioactivity in urine was 94%, with 5% of the radioactive dose recovered in feces.

Apparent oral clearance (CL/F) of gabapentin from plasma after dosing of GEn with food ranged from 6.0 to 9.3 L/hr. Following oral dosing of GEn, plasma clearance of gabapentin is approximately proportional to creatinine clearance. Renal clearance (CLr) of gabapentin ranged from 5 to 7 L/hr, regardless of food intake or food type. The elimination half-life (t½) of gabapentin ranges from 5.1 to 6.0 hours and is unaltered by dose or following multiple doses of GEn.

Special Populations
Race: In the population pharmacokinetic study, the majority (94%) of subjects in the clinical studies were Caucasian, and no single other race was greater than 4%; therefore, the effect of race could not be studied.

Gender: There are no clinically meaningful differences in pharmacokinetics of GEn between male and female patients.

Geriatric Patients: There are no clinically significant differences in pharmacokinetics of GEn between geriatric patients (≥65 years of age) and younger patients (18 to <65 years of age). However, the pharmacokinetics in geriatric patients may be affected by an age-related decline in renal function.

Renal Impairment: Gabapentin clearance after dosing with GEn is approximately proportional to CrCl. Apparent oral clearance (CL/F) decreased in moderate (4.2 L/hr) and severe renal impairment patients (1.7 L/hr) compared with 6.0 to 9.3 L/hr in patients without renal impairment. Similarly, CLr was decreased to 3 and 1 L/hr in moderate and severe renal impairment patients, respectively, compared with 5 to 7 L/hr in non-renal impairment patients. Dosage reduction in patients with renal dysfunction not on dialysis is necessary. For patients on hemodialysis, treatment with GEn is not recommended.

Drug Interactions
Cimetidine: Gabapentin released from GEn is eliminated by renal clearance via OCT2. Cimetidine is a known substrate for this same elimination pathway. Coadministration of 1,200 mg of GEn once daily with cimetidine 400 mg 4 times daily showed no effect on cimetidine exposure. There was an increase in AUC of gabapentin (24%) and a decrease in renal clearance of gabapentin (20%); these effects are not expected to be clinically relevant. No clinically relevant pharmacokinetic interactions are expected between GEn and other substrates of OCT2.

Naproxen: The pathway for absorption of GEn includes active transport via a proton-linked MCT-1. Coadministration of 1,200 mg of GEn once daily with naproxen 500 mg twice daily, a known substrate of MCT-1, showed no effect on naproxen exposure or steady-state gabapentin Cmax and AUC. No clinically relevant pharmacokinetic interactions are expected between GEn and other substrates of MCT-1.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program for PHN includes 17 Phase I studies and 3 Phase 2 PHN studies summarized in Table 3. The Phase I studies were all previously submitted to the RLS NDA.

Table 3: Clinical Studies in the PHN Clinical Development Program

Study Number[1]	Status of Study	Type of Study	Total Number of Randomized/ Assigned Subjects
Phase I/Clinical Pharmacology Studies – Healthy Subjects			
Human PK Studies			
XP006	Complete	Single dose safety and PK IR formulation	50
XP018	Complete	Multiple dose safety and PK IR formulation	38
XP065	Complete	Single dose ADME	6
XP069	Complete	Single dose safety and PK	32
Comparative Bioavailability Studies			
XP019	Complete	Single dose relative bioavailability (IR and ER)	24
XP044	Complete	Single dose relative bioavailability and food effect	36
XP057	Complete	Single dose relative bioavailability	12
XP086	Complete	Single dose in vitro in vivo correlation (IVIVC)	10
PXN110882	Complete	Single-dose, relative bioavailability, safety and tolerability	17
Food Effect Studies			
XP022	Complete	Single dose food effect	12
XP087	Complete	Single dose food effect	12
Drug Interaction Studies			
XP067	Complete	Naproxen drug interaction	12
XP068	Complete	Cimetidine drug interaction	12
Intrinsic Factors Studies			
XP066	Complete	Renal impairment	15
XP072	Complete	Single dose safety and PK, Japanese and Caucasian subjects	48
XP073	Complete	Multiple dose safety and PK Japanese subjects	31
Thorough QTc Study			
XP078	Complete	Thorough QT	54
Phase II Clinical Studies – PHN Subjects			
PXN110748	Complete	DB, randomized, placebo-controlled, parallel group	376
XP009	Complete	DB, randomized, placebo-controlled, parallel group	102
PXN110527	Complete	DB, randomized, two-period, crossover	96

ADME: absorption, distribution, metabolism, excretion; DB: double-blind; ER: extended-release; IR: immediate-release; PHN: postherpetic neuralgia; PK: pharmacokinetic
Note: All studies used the ER formulation unless otherwise noted. Study XP065 used a capsule radiolabeled formulation.
1. Study numbers with prefix of 'XP' were Xenoport-sponsored studies. Study numbers with prefix of 'PXN' were GSK-sponsored studies.

Source: Table 2: Clinical Studies Providing Primary and Supportive Safety Information for GEn in PHN Clinical Development Program. Clinical Overview, p. 13

5.2 Review Strategy

Efficacy

Study PXN110748 was the principle study submitted by the Applicant to support the efficacy of GEn for the relief of PHN pain in adults. Supporting data for efficacy and safety provided by Studies XP009 and PXN110527 and two published articles describing efficacy studies conducted in the Neruontin registration program were also submitted by the Applicant.

Safety
GSK's safety analyses included safety data from studies PXN110748, XP009 and PXN110527. These studies were analyzed separately due to differences in study design and duration of treatment (i.e., two week study duration for XP009 and no placebo control for PXN110527). The safety findings are reviewed and discussed in Section 7 on Safety.

5.3 Discussion of Individual Studies/Clinical Trials

To support efficacy for this 505(b)(2) application, the Applicant submitted the following studies that are reviewed below: principal efficacy study (PXN110748); supporting efficacy studies PXN110527 and XP009; and two published articles describing the two efficacy trials used in the Neurontin registration program.

5.3.1 PXN110748

The following summary of the design of Study PXN 110748 was derived from the revised protocol incorporating amendment #1 dated January 7, 2008. This amendment was enacted prior to study initiation. The original protocol was dated October 15, 2007 and was amended three times. Amendment 2 was added March 3, 2008 and Amendment 3 was added October 17, 2008. Relevant changes to the protocol related to Amendments 2 and 3 are included in italics.

Title: Study PXN110748: An efficacy and safety study of XP13512 compared with a concurrent placebo control in subjects with neuropathic pain associated with postherpetic neuralgia (PHN)

Note: Compound number XP13512 is GEn. Throughout the remainder of this protocol review compound number XP13512 will be referred to as GEn.

Dates Conducted: The study was initiated 06 February 2008 and completed 29 July 2009.

Objectives

The primary objectives were:
- To investigate the efficacy of GEn to reduce pain, to improve physical and emotional function, and to assess global improvement
- To evaluate the safety of GEn

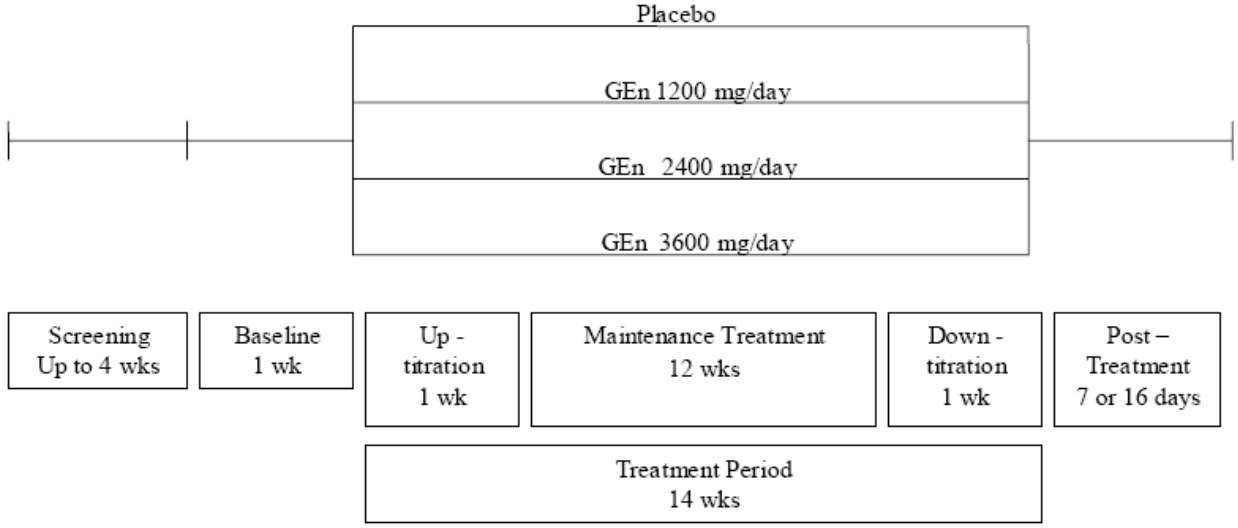
The secondary objective was to:
- Estimate the systemic exposure of gabapentin associated with the following GEn doses: 1200 mg/day, 2400 mg/day, and 3600 mg/day

The exploratory objectives were to:

- To investigate the exposure-response relationship of GEn
- To investigate a potential relationship between subject's expectation of pain response prior to treatment and the placebo response
  - To investigate the effect of GEn on the duration of sleep and the frequency of awakenings during sleep
  - To investigate a possible genetic relationship to the response to GEn

Overall Design: This was a Phase 2b, multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of three doses of GEn in subjects with neuropathic pain associated with PHN. The study was to have consisted of 6 phases (Figure 1): screening (up to 28 days), baseline including randomization (7 days), up-titration (7 days), maintenance treatment at a fixed dose (12 weeks), down-titration (7 days), post-treatment (7 days after the last dose or 16 days for females of childbearing potential). Eligibility criteria included a diagnosis of PHN for at least three months and a baseline 24-hour average pain intensity score of ≥ 4.0. The baseline score was calculated as the mean of at least four daily scores during the 7 days prior to randomization. Eligible subjects were to have been randomized in a ratio of 1:1:1:1 to receive: oral GEn 3600 mg/day, GEn 2400 /day, GEn 1200 mg/day, or matching placebo.

Figure 1: Study Design of PXN110748



Reference: Figure 1. Study Design, Clinical Study Report PXN 110748, p. 18

Inclusion Criteria:

Patients were to have met the following criteria:

1. Outpatient subjects aged 18 years or older.
2. Female subjects of non-childbearing potential or for females of childbearing potential: not lactating, negative pregnancy test ≤7 days prior to study treatment and agree to use effective contraception.
3. Diagnosis of PHN of at least three months duration prior to screening (i.e., pain present for at least three months from the healing of a herpes zoster skin rash).
4. A baseline 24-hour average pain intensity score ≥4.0 based on an 11-point NRS. Baseline score calculated as the mean of the daily scores during the 7 days prior to randomization (at least four assessments of the daily 24-hour average pain score must have been recorded during the seven-day Baseline Period).
5. Able to provide written informed consent.

Exclusion Criteria:

Patients were to have been excluded if any of the following applied:

1. Has other chronic pain conditions not associated with PHN. However, the subject was not to have been excluded if all the following criteria applied:
   - The pain is located at a different region of the body
   - The pain intensity is not greater than the pain intensity of the PHN
   - The subject can assess PHN pain independently of the other pain condition
2. Unable to discontinue prohibited medications, non-drug therapies or procedures for the relief of pain of PHN.
3. Has any of the following medical conditions, laboratory abnormalities or disorders:
   - Hepatic impairment defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2x upper limit of normal (ULN), or alkaline phosphatase or bilirubin >1.5x ULN
   - Chronic hepatitis B or C with a positive Hepatitis B surface antigen (HBsAg) or Hepatitis C Core Antigen Antibody (Hep C antibody)
   - Impaired renal function defined as either creatinine clearance <60 mL/min (estimation of creatinine clearance by Cockroft and Gault Method) or renal dysfunction requiring hemodialysis
   - Corrected QT (QTc) interval ≥450 msec (based on single or average QTc value of triplicate electrocardiograms (ECGs) obtained over a brief recording period)
   - QTc interval ≥480 msec for patients with Bundle Branch Block
   - Uncontrolled hypertension at screen defined as sitting systolic blood pressure >160 mmHg and/or sitting diastolic blood pressure >90 mmHg

- Current diagnosis of active epilepsy or any active seizure disorder requiring chronic therapy with antiepileptic drugs
- Medical condition or disorder that would interfere with the action, absorption, distribution, metabolism, or excretion of GEn

4. Meets criteria as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) for a major depressive episode or for active significant psychiatric disorders within last year, including dementia, general anxiety disorder, psychosis or bipolar disorder.
    - Subjects with a history of depression that is in remission, with or without antidepressant treatment, may participate, unless a stable antidepressant regimen includes a prohibited medication.
    - Antidepressant medication may not be changed or discontinued to meet entry criteria and must be stable for at least three months prior to the start of the Baseline Period.
5. Has a history of clinically significant drug or alcohol abuse as defined by DSM-IV-TR or is unable to refrain from substance abuse throughout the study. Benzodiazepines or atypical benzodiazepines prescribed as hypnotic sleep agents are permitted.
6. Is currently participating in another clinical study in which the subject is, or will be exposed to an investigational or non-investigational drug or device.
7. Has participated in a clinical study in which the subject was exposed to an investigational or non-investigational drug or device within the preceding month for studies unrelated to the current illness, or within the preceding six months for studies related to the current illness.
8. Has been treated previously with GEn.
9. Has a history of an allergic reaction, or a medically significant adverse reaction to the investigational products (including gabapentin), their excipients, acetaminophen, or compounds closely related to acetaminophen.

Study Medication

GEn oral sustained release tablets containing 600 mg of GEn and identical placebo were to have been administered with food.

Concomitant Therapy

Rescue Analgesia
Subjects were to have been permitted to take acetaminophen 500 mg up to a maximum dose of 3000 mg per 24-hour period as needed for rescue analgesia. *This maximum dose of 3000 mg per 24-hour period includes acetaminophen in any opioid combination product that the subject may be taking (Amendment 3).* Subjects were to have been instructed not to take any rescue analgesia within 12 hours before a clinic visit.

Permitted Medications

In order to be eligible for participation in the trial, subjects were not allowed to take more than one medication from each of the following classes: nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and tricyclic antidepressants (Amendment 3).

- NSAIDs including cyclooxygenase-2 (COX-2) inhibitors were to have been allowed [redacted] (b) (4) *(removed in Amendment 3)* provided that their use was in a stable pattern (≥4 weeks) prior to screening and that it would remain stable. NSAIDs, including COX-2 inhibitors, were to have been allowed for transient acute pain during the study if all the following circumstances were met:
  - Use in response to a self-limited isolated musculoskeletal injury or inflammation that was not related to the target pain under study
  - Not used during the Baseline Period or during the last two weeks of the Maintenance Treatment Period
  - Not used for more than 7 days in total duration
  - Use was not repeated for the same injury and any two periods of use must be separated by at least two weeks
  - Dose and route were used in accordance with package label

The following medications were to have been permitted provided they were taken as a stable dose prior to screening, and that the dose remained stable throughout the subject's participation in the study:

- Aspirin at doses ≤325 mg/day
- *Opioids at doses ≤90 mg/day morphine equivalent; opioid and simple analgesic combination products (e.g., acetaminophen and codeine, acetaminophen and hydrocodone, ibuprofen and oxycodone, etc)(Amendment 3)*
- *Tramadol and tramadol/acetaminophen combination products (Amendment 3)*
- *Tricyclic antidepressants (Amendment 3)*
- Selective serotonin reuptake inhibitors for depression *provided that they are taken as a stable regimen for at least three months (Amendment 3)*
- Benzodiazepines or atypical benzodiazepines used at stable bedtime dose for sleep provided the duration of use had been at least 3 months prior to screening
- Topical analgesics if used at locations other than the site of the target pain

Prohibited Medications

The following medications were to have been prohibited and discontinued at least 14 days prior to the Baseline Visit and throughout the duration of the study:

- Anticonvulsants (e.g., gabapentin, lamotrigine, carbamazepine, pregabalin)
- [redacted] (b) (4) *(Deleted in Amendment 3)*

- Atypical antidepressants such as serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine, duloxetine), tetracyclic antidepressants, norepinephrine-dopamine reuptake inhibitors (e.g., bupropion), and trazodone
- Aspirin at doses >325 mg/day and other salicylates
- Benzodiazepines or atypical benzodiazepines, unless used at bedtime for sleep
- Dextromethorphan used for pain at doses >120 mg/day or dextromethorphan when combined with quinidine
- Herbal medications for pain including marijuana
- Mexiletine HCl
- [redacted] *(Deleted in Amendment 3)*
- [redacted] *(Deleted in Amendment 3)*
- *Opioids at doses >90 mg/day morphine equivalent (Amendment 3)*
- Topical analgesics (including lidocaine) used for PHN or if applied to the same area of body as the PHN

The following medications were to have been prohibited and discontinued at least 28 days prior to the Baseline Visit:

- Adenosine
- Topical capsaicin used for PHN or if applied to the same area of body as the PHN
- Intrathecal peptides including Prialt (ziconotide intrathecal infusion)

Prohibited procedures:

- Nerve blocks or acupuncture performed within four weeks of randomization
- Transcutaneous Electrical Nerve Stimulation (TENS) performed within 14 days of randomization (TENS administered at different site from target pain allowed)

Study Procedures

A schedule of assessments is contained in Table 4.

Table 4: Schedule of Assessments

Study Period		Screen[a]	Base-line[a]	Rando-mization	Treatment (Up-titration)	Treatment Maintenance							Down-titration (T2) Visit	Withdrawal (WD)	Post-Treatment
Endpoint	Study Visit	S1	B1	R	T1	M1	M2	M3	M4	M5	M6	M7	T2	WD	PT1[f]
	Study Day	-35 to -7	-7	0	7	14	21	35	49	63	77	91	98		T2 +7 or WD +14
	Study Week[b]	-5 to -1	-1	0	1	2	3	5	7	9	11	13	14		15
	Clinic Visit	√	√	√	√	√		√		√		√	√	√	√
	Phone Contact						√		√		√				
Eligibility	Informed Consent	√	√[c]												
	I/E Criteria	√	√	√											
Safety	Medical Hx	√	√[c]												
	PE[i]	√	√[c]										√	√	√
	Vital Signs	√	√[c]	√	√	√		√		√		√	√	√	√
	Body Weight		√		√	√		√		√		√	√	√	
	Pedal Edema		√		√	√		√		√		√	√	√	
	ECG[d]	√	√[c]			√		√		√		√		√	√[e]
	Clinical Chemistry	√	√[c]			√		√		√		√		√	√
	Hematology	√	√[c]			√		√		√		√		√	√
	Urinalysis	√	√[c]			√		√		√		√		√	√
	HBsAg & Hep C antibody	√	√[c]												
	Pregnancy Test	√	√[c]	√		√		√		√		√		√	√[g]
	Concomitant meds			√	√	√		√		√		√	√	√	√
	Record AEs			√	√	√	√	√	√	√	√	√	√	√	√
	Record SAE	√[l]	√	√	√	√	√	√	√	√	√	√	√	√	√
IP	Dispense IP			√	√			√		√		√		√[j]	
Treatment	PI-NRS[h]		√	√	√	√	√	√	√	√	√	√	√	√	√
Efficacy	NPS & SF-MPQ			√		√		√		√		√		√	
	Rescue Med[h]		√	√	√	√	√	√	√	√	√	√	√	√	
	Allodynia			√		√		√		√		√		√	√
	BPI			√		√		√		√		√		√	
	SF-36			√		√		√		√		√		√	
	Sleep [h]		√	√	√	√	√	√	√	√	√	√	√	√	
	POMS			√		√		√		√		√		√	
	PGIC/CGIC					√		√		√		√		√	
Others	Subject expectation			√											
	PK/PD					√		√		√		√		√	
	PGx			√[k]											

a. Subjects not taking prohibited medications or non-drug therapies may begin study at Baseline Visit
b. Study week refers to the end of the week; within clinic visit window for that week will be (+) or (-) 7 days
c. Procedure will be performed only if the subject did not have a Screening Visit or the procedure was not performed at the time of a Screening Visit
d. Three 12-lead ECGs taken approximately one minute apart will be obtained at Screening. A single ECG will be obtained at all relevant on-treatment visits. If an ECG is not scheduled at next clinic visit, repeat ECG at next scheduled clinic visit only if clinically indicated
e. Procedure performed only if clinically indicated, i.e. if a new clinically relevant change from baseline occurs during the study
f. All subjects will undergo a Post-treatment Visit (PT1) and this PT1 Visit will be 7 days after the date of the last study medication administration. This would be 7 days from the T2 Visit (T2 + 7) or 14 days from the WD Visit (WD + 14) as the latter visit starts the 7 days of down-titration to the last dose and the PT1 Visit is another 7 days from that last dose.
g. The final pregnancy test required for females of child bearing potential (FCBP) will occur 16 days after the last dose of investigational product. Centers will follow-up with subjects via phone call to document the result of the pregnancy test.
h. Pain intensity and sleep interference, total sleep time, awakenings and rescue medication usage will be measured daily. Note that only pain intensity (PI-NRS) is measured at the Post-treatment Visit (PT1).
i. Includes measurement of height at Screening or Baseline Visit only.
j. A subject who is prematurely withdrawn from the study should be down-titrated from study drug if at all possible using the schedule specified in Table 4. A subject who misses 3 consecutive days of dosing should be withdrawn from the study. Such a subject would not need a down-titration kit, and is not required to return for a PT1 Visit 7 days after the last dose of study drug was taken.
k. It is recommended that the PGx blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.
l. SAEs related to study participation ONLY should be recorded at this time point.

Abbreviations: AE: Adverse Event; ECG: electrocardiogram; BPI: Brief Pain Inventory; HBsAg : Hepatitis B surface antigen; Hep C antibody: Hepatitis C Core Antigen antibody; Hx: History; I/E: Inclusion/Exclusion; IP: Investigational product; Med: Medication; NPS: Neuropathic Pain Scale score; PE: physical examination; PK/PD: Pharmacokinetic/Pharmacodynamic; PGIC/CGIG: Patient/Clinician Global Impression of Change Questionnaire; PGx: pharmacogenetics; PI-NRS: Pain Intensity Numerical Rating Scale; POMS: Profile of Mood States scale; SAE: Serious Adverse Event; SF-36: Short Form-36 Form; SF-MPQ: Short-Form McGill Pain Questionnaire

Source: Table 5. Time and Events Table, Protocol PXN 110748 Amendment 1, p. 35

Written informed consent was to have been obtained prior to performing any of the assessments. Study subjects were to have entered their data into an electronic patient diary (e-diary). The following assessments were to have been recorded in the e-diary each day: time of administration of study medication, daily rescue medication use (the number of 500 mg acetaminophen tablets taken), pain score, Sleep Interference numeric rating scale (NRS) score, total sleep time and sleep awakenings. Additional outcome measures were to have been completed by the subject at the clinic using the e-diary (Table 4).

Drug Administration

Subjects were to have taken GEn or matching placebo tablets with food once in the morning and once at night. For subjects missing three consecutive days of dosing, (s)he should have been withdrawn from the study. Subjects were to have been up titrated to the maintenance dose of GEn over seven days (Table 5). Subjects were to have been allowed rescue analgesia with acetaminophen 500 mg up to a maximum dose of 3000 mg but were not to have taken any rescue medication within 12 hours before a clinic visit.

Table 5: XP13512 Up-titration Schedule

Study Drug	Dose Time	Seven-Day Up-titration Period							Maintenance Treatment
		D1	D2	D3	D4	D5	D6	D7	D8
PBO	AM	□□□	□□□	□□□	□□□	□□□	□□□	□□□	□□□
	PM	□□□	□□□	□□□	□□□	□□□	□□□	□□□	□□□
XP13512 1200 mg/day	AM	■□□	■□□	■□□	■□□	■□□	■□□	■□□	■□□
	PM	□□□	□□□	□□□	■□□	■□□	■□□	■□□	■□□
XP13512 2400 mg/day	AM	■□□	■□□	■□□	■□□	■■□	■■□	■■□	■■□
	PM	□□□	□□□	■□□	■□□	■■□	■■□	■■□	■■□
XP13512 3600 mg/day	AM	■□□	■□□	■□□	■□□	■■□	■■□	■■■	■■■
	PM	□□□	□□□	■□□	■□□	■■□	■■□	■■■	■■■

■: DRUG XP13512 600 mg tablet
□: DRUG placebo tablet

Source: Table 3. Investigational Product Administration – Up-titration, Protocol PXN 110748 Amendment 1, p. 28

At the end of treatment subjects were to have been tapered off study drug over one week (Table 6).

Table 6: XP13512 End of Treatment Taper Schedule

Study Drug	Dose Time	Maintenance Treatment	Six-Day Down-titration Period						End of Treatment
		D91	D92	D93	D94	D95	D96	D97	D98
PBO	AM	□□□	□□□	□□□	□□□	□□□	□□□	□□□	0
	PM	□□□	□□□	□□□	□□□	□□□	□□□	□□□	0
XP13512 1200 mg/day	AM	■□□	■□□	■□□	■□□	■□□	■□□	■□□	0
	PM	■□□	■□□	■□□	■□□	□□□	□□□	□□□	0
XP13512 2400 mg/day	AM	■■□	■■□	■■□	■□□	■□□	■□□	■□□	0
	PM	■■□	■■□	■■□	■□□	■□□	□□□	□□□	0
XP13512 3600 mg/day	AM	■■■	■■□	■■□	■□□	■□□	■□□	■□□	0
	PM	■■■	■■□	■■□	■□□	■□□	□□□	□□□	0

■: DRUG XP13512 600 mg tablet
□: DRUG placebo tablet

Source: Table 4. Investigational Product Administration – Down-titration, Protocol PXN 110748 Amendment 1, p. 29

Efficacy Assessments/Endpoints

The following efficacy assessments were to have been performed:

Primary Efficacy Assessment/Endpoint

- Change from baseline to end of treatment with respect to the mean 24-hour average pain intensity score based on an 11-point NRS (0 = "no pain" and 10 = "pain as bad as you can imagine")
    - The 24-hour average pain intensity score was to have been the subject's assessment of their average pain intensity over the preceding 24 hours
    - The mean baseline score was to have been the calculated mean of the daily scores during the 7 days prior to randomization
    - The mean end of treatment score was to have been the calculated mean of the daily scores during the last 7 days of the maintenance treatment

Secondary Efficacy Assessments/Endpoints

- Percent of subjects achieving 10%, 20%, 30%... reduction in the 24-hour average pain intensity
- Time to onset of sustained improvement in the 24-hour average pain intensity defined as a reduction of ≥2 points from baseline for ≥2 consecutive days
- Day-time average pain intensity score recorded in the evening before bedtime and defined as the time between rising in the morning and going to bed at night
- Night-time average pain intensity score recorded in the morning upon awakening and defined as the time between going to bed at night and rising in the morning
- Current pain intensity score recorded in the morning upon awakening and in the evening before bedtime

- Day-time worst pain intensity score recorded in the evening before bedtime
- Night-time worst pain intensity score recorded in the morning upon awakening
- Sleep interference score recorded in the morning upon awakening. The sleep interference score is the subject's assessment of sleep interference due to pain
- NPS pain quality questionnaire
- SF-MPQ Questionnaire
- Patient and clinician global impression of change
- Dynamic allodynia (response to a standardized light touch stimulus, a foam brush applied with light pressure to the site of maximum pain)
- Rescue analgesic use based on number of 500 mg acetaminophen tablets used
- Physical functioning derived from BPI questionnaire
- Quality of life measured on SF-36
- Emotional functioning measured on POMS Questionnaire

Pharmacokinetic/Pharmacodynamic Assessments

The following secondary pharmacokinetic parameters were to have been obtained:

- $C_{max, ss}$: Maximum plasma concentration of gabapentin (between 6 and 8 hours post-dose) at steady state
- $C_{min, ss}$: Minimum plasma concentration of gabapentin at 12 hours post-dose at steady state
- $C_{avg, ss}$: Average daily plasma concentration of gabapentin at steady state calculated as $AUC_{0-24, ss}$ / 24 hours.
- $AUC_{0-24, ss}$: Daily (24-hour) area under the plasma concentration-time profile for gabapentin at steady state (= 2 x $AUC_{0-12, ss}$).

The exploratory PK/PD endpoint analysis was to have been the relationship between the 24-hour average pain intensity score and gabapentin exposure ($C_{max, ss}$; $C_{min, ss}$; $C_{avg, ss}$; $AUC_{0-24, ss}$)

Safety Assessments

The following pre-specified safety assessments were to have been performed:

- Treatment emergent adverse events (TEAEs)
- Possible suicidality-related adverse events: This may include an event that involves suicidal ideation, a preparatory act, a suicide attempt or a completed suicide.
- Clinical laboratory evaluations: The following blood chemistry and hematology analyses were to have been performed (Table 7):

Table 7: Clinical Laboratory Evaluations Study PXN10748

Hematology	Blood Chemistry	Immunology
White Blood Cell (WBC) count with differential	Sodium, Potassium, Chloride, Calcium	HBsAg (Hep B core antibody)
Bands, Neutrophils, Lymphocytes	Phosphorus (inorganic), Bicarbonate, Urea Nitrogen	Hep C antibody
Monocytes, Eosinophils, Basophils	Creatinine, Bilirubin (total)	
Hemoglobin	Aspartate aminotransferase (AST, previously SGOT)	
Hematocrit	Alanine aminotransferase (ALT, previously SGPT)	
Red Blood Cell (RBC) count	Alkaline Phosphatase (ALP), Glucose (non-fasting)	
Platelet Count	Protein (Total), Albumin, Total Cholesterol	
Mean Corpuscular Volume (MCV)		

Source: Protocol PXN110748 Amendment 1, p. 47

Serum creatine phosphokinase (CPK) was added to the clinical chemistry panel in Amendment 2.

- Urinalysis (pH, blood and protein) were to have been performed
- Vital signs (blood pressure, heart rate)
- ECG measurements: Three 12-lead ECGs were to have been taken approximately one minute apart at screening or baseline in order to ensure minimum variability with baseline recordings. The average of the ECG intervals on the 3 readings was to have been used to determine whether the subject was eligible for study enrollment. Subsequently, a single ECG was to have been taken at all relevant treatment visits. If an on-treatment ECG revealed QT prolongation, then the ECG would be repeated 2 more times. The average of the intervals of the 3 readings was to have been used to decide whether to discontinue the subject. Conduction intervals were to have been confirmed by an external cardiologist/vendor and entered into the database. A photocopy of the ECGs was to have been placed in the subject's source documents. For any abnormal ECG changes a follow-up was to have been scheduled.
- Physical Examination
- Body weight
- Pedal edema: An assessment for pedal edema was to have been performed by firmly pressing the thumb anterior to the subject's ankle until further pressure produced no greater indentation. The worst affected ankle was to have been assessed at screening and then at prespecified times throughout the study. The

depth of the pit was to have been visually estimated and graded using the 5 point scale below (Table 8).

Table 8: Pedal Edema Scale

Grade	Estimated Depth of Indentation
0	<1 mm
1	1-2 mm
2	3-5 mm
3	6-10 mm
4	> 10 mm

Source: Protocol PXN110748 Amendment 1, p. 47

- Pregnancy testing from Screening Visit to 16 days after the last dose of study medication. The 16-day, post-dose period is derived from the sum of the time required for complete elimination of the drug from the body (5 half-lives or 2 days) and the minimum time from conception before the urine test can detect pregnancy (14 days).

Withdrawal Criteria

The following were to have been discontinuation criteria:

- Abnormal liver function tests:
  1. ALT ≥3xULN and bilirubin ≥1.5xULN
  2. ALT ≥5xULN
  3. ALT ≥3xULN if associated with hepatitis or rash
  4. ALT ≥3xULN persists for ≥4 weeks
  5. ALT ≥3xULN and cannot be monitored weekly for 4 weeks
- Voluntarily discontinues study participation (consent withdrawal)
- Discontinued by the investigator, at his/her discretion
- A serious or life-threatening AE
- A subject missing 3 consecutive days of dosing
- Extensive deviation from the protocol
- Lost to follow-up
- Treatment blind is broken
- Subject becomes pregnant
- *Subject has a serum creatine phosphokinase (CPK) level >10 x ULN (Amendment 2)*
- Meets following ECG criteria based on average QTc value of triplicate ECGs:
  - QTc >500 msec or uncorrected QT >600 msec
  - Bundle branch block QTc >530 msec

Statistical Methods

Analysis Populations

Intent-to-Treat Population

The Intent-to-Treat (ITT) Population was defined as all randomized subjects who took at least one dose of study drug and provided at least one post-baseline efficacy measurement. The ITT Population was to have been used to assess all efficacy endpoints and health outcomes endpoints.

Per-Protocol Population

The Per Protocol (PP) Population was defined as those members of the ITT Population who have no major protocol deviations. The major protocol deviations leading to exclusion from the PP Population were to be defined in the Reporting and Analysis Plan (RAP) prior to unblinding. The PP Population was not to have been analyzed if this population comprised more than 95% or less than 50% of the ITT Population. The analysis of the PP Population was to have provided supportive evidence of the analysis of the ITT Population. Only the primary efficacy variable was to have been analyzed using the PP Population.

Safety Population

The Safety Population was defined as all randomized subjects who took at least one dose of study drug.

Pharmacokinetics Population

The PK Population was defined as all randomized subjects who took at least one dose of study drug and had at least one PK sample taken.

Statistical Analysis

Primary Efficacy Analysis

The primary comparisons of interest were to have been the change from baseline to end of treatment with respect to the mean 24-hour average pain intensity score based on the 11-point NRS for:

- GEn 3600 mg/day vs. placebo
- GEn 2400 mg/day vs. placebo
- Gen 1200 mg/day vs. placebo

Comparison of each GEn dose vs. placebo was to have been performed on the ITT Population using the LOCF dataset. These analyses were to have been carried out using a step-down procedure that used Dunnett's test within a closed testing scheme for multiple comparisons with a common control to maintain the overall experiment-wise alpha level of 0.05.

The step-down procedure that uses Dunnett's test within a closed testing scheme for 3 multiple comparisons was to have been conducted as follows:

1. The test statistics for each treatment dose vs. the common control are calculated and ordered $T_{(1)} \leq T_{(2)} \leq T_{(3)}$;
2. The critical values for Dunnett's test, $C_{(0.05,1)}$, $C_{(0.05,2)}$, $C_{(0.05,3)}$ are calculated;
3. If $T_{(3)} \leq C_{(0.05,3)}$, then all testing stops and none of the active treatments are statistically significantly different than the common control;
4. If $T_{(3)} > C_{(0.05,3)}$, then the corresponding treatment is significantly different than placebo, and testing can continue such that next $T_{(2)}$ is compared to $C_{(0.05,2)}$.

The primary efficacy endpoint was to have been change from baseline to end of treatment with respect to the mean 24-hour average pain intensity score based on the 11-point NRS. The mean score was to have been the calculated mean of the daily 24-hour average pain scores for each subject during the last 7 days of the Maintenance Treatment Period. These data were to have been summarized and analyzed for the ITT Population using LOCF scores. Each dose of GEn was to have been compared to placebo using an analysis of covariance (ANCOVA) model, with body mass index (BMI), baseline pain intensity score, center grouping and treatment as terms in the model. A step-down procedure that uses Dunnett's test within a closed testing scheme for multiple comparisons with a common control was to have been used to maintain the overall experiment-wise alpha level of 0.05.

In a separate, secondary supportive analysis interaction between treatment and each of the covariates, BMI, baseline pain intensity score, and center grouping, were to have been investigated for the primary efficacy endpoint. Interactions were to have been tested at the 10% significance level, and significant interactions investigated. The primary analysis model was not to have included interaction terms regardless of significance.

Secondary Efficacy Analyses

The secondary efficacy endpoints and their associated analysis methods were to have been the following:

- The change from baseline in the mean: 24-hour average pain intensity score, day-time average pain intensity score, night-time average pain intensity score, current pain intensity score, day-time worst pain intensity score, night-time worst pain intensity score, sleep interference score, and rescue analgesia consumption (mg) were to have been analyzed at each week of treatment and post-treatment. These data were to have been analyzed for the ITT Population using LOCF scores. Analysis was to have been conducted as per the primary, but without adjustment for multiplicity. If a treatment by covariate interaction was found to be significant and meaningful in the primary analysis, then the interaction was to have been

explored for these secondary analyses. Otherwise, no investigations of interactions were to have been conducted on the secondary efficacy endpoints.

- The change from baseline to each week of assessment with respect to: Pain quality as assessed by the NPS and the SF-MPQ, and Dynamic allodynia response to a standardized light touch stimulus were to have been summarized and analyzed for the ITT Population using LOCF scores at each week of treatment. Analysis was to be conducted as per the primary, but without adjustment for multiplicity. As for other secondary endpoints, treatment by covariate interaction was only to be explored if it was found to be significant and meaningful in the primary analysis.

- The proportion of subjects who are "much improved" or "very much improved" on each of the PGIC and CGIC questionnaires at each assessment were to have been analyzed using logistic regression with center group and treatment as terms in the model. The parametric assumptions of the model was to have been assessed, and if appropriate, a Cochran-Mantel-Haenzel (CMH) chi-square test conducted.

- The proportion of subjects achieving various levels of percent reduction from baseline in the mean 24-hour average pain intensity score (responder rate) at each week of treatment was to have been summarized and analyzed as described for PGIC.

- The time to onset of sustained improvement in the 24-hour average pain intensity score (where sustained improvement is defined as a reduction of ≥2 points from baseline for ≥2 consecutive days) was to have been analyzed using the Kaplan-Meier survival analysis.

No closed testing procedure or alpha adjustment was to have been applied to the statistical analyses because the study was not powered for testing secondary endpoints and all p-values presented for secondary endpoints were to have been interpreted only as summary statistics

Protocol Amendments:

Original Protocol, October 15, 2007
No subjects were enrolled under this protocol.

Amendment #1, January 7, 2008
The preceding protocol review was based on Protocol Amendment 1. The first subject was screened under this amended protocol. Amendment 1 provided the following changes:

- Clarification in wording and correction of errors from the original protocol

- Withdrawal criteria for subjects missing three consecutive days of dosing
- Collection of information on any subject that experiences a possible suicidality-related adverse event
- Establishment of an internal Safety Review Committee, consisting of GSK personnel who are not involved in the conduct of this study

Amendment #2, March 3, 2008

Amendment 2 included the following changes:

- Addition of CPK to the chemistry panel
- Withdrawal criteria for CPK level >10 x ULN

Amendment #3, October 17, 2008

Amendment 3 included the following changes:

- Addition to the exclusion criteria that the validity of a positive hepatitis C antibody test result should be confirmed by a RIBA® test before excluding the subject
- Addition to the inclusion criteria that subjects can not take more than one medication from each of the following classes: NSAIDs, opioids, and tricyclic antidepressants
- Clarification that the maximum dose of 3000 mg of acetaminophen per 24-hour period included any opioid combination product that the subject may be taking
- Allowed the following medications:
    - Opioids ≤90 mg/day morphine equivalent; opioid and simple analgesic combination products (e.g., acetaminophen and codeine, acetaminophen and hydrocodone, ibuprofen and oxycodone, etc.)
    - Tramadol and tramadol/acetaminophen combination products
    - Tricyclic antidepressants
    - NSAIDs and COX-2 inhibitors allowed for indications other than osteoarthritis

Study Results

Enrollment/Randomization

A total of 376 subjects were randomized in 72 centers in the US and Canada. The Applicant reports that there was imbalance in the total number of subjects randomized to each treatment group due to the fact that subjects were randomized within center, in blocks of 8, and 81% of sites randomized fewer than 8 subjects. This resulted in the GEn 1200 mg treatment group having more randomized subjects and the GEn 2400 mg treatment group having fewer randomized subjects (Table 9).

Table 9: Summary of Subject Disposition (Randomized Subjects, PXN110748)

Subject Status	Number (%) of Subjects				
	PBO- N =95	GEn 1200 mg N =107	GEn 2400 mg N =84	GEn 3600 mg N =90	Total N =376
Completion Status					
Completed	64 (67)	85 (79)	60 (71)	56 (62)	265 (70)
Withdrawn	31 (33)	22 (21)	24 (29)	34 (38)	111 (30)
Primary Reason[1] for Withdrawal					
Adverse event	12 (13)	6 (6)	12 (14)	16 (18)	46 (12)
Lack of efficacy	6 (6)	1 (<1)	1 (1)	4 (4)	12 (3)
Protocol Deviation	5 (5)	4 (4)	4 (5)	9 (10)	22 (6)
Lost to Follow-Up	1 (1)	2 (2)	0	1 (1)	4 (1)
Investigator Discretion	2 (2)	2 (2)	2 (2)	0	6 (2)
Consent withdrawn	5 (5)	7 (7)	5 (6)	4 (4)	21 (6)

Data Source: Table 1.1
1. Subjects may have only one primary reason for withdrawal.
Source: Clinical Study Report, Protocol PXN110748, p. 41

Subject Disposition
A total of 29% (80/281) of subjects in the GEn treatment groups and 33% (31/95) of subjects in the placebo treatment group prematurely discontinued study drug (Table 9). However, more subjects discontinued study from the GEn 3600 mg treatment group 38% (34/90) than from any other treatment group. The GEn 3600 mg treatment group had the most discontinuations due to adverse events 18% (16/90) compared to GEn 2400 mg 14% (12/84), GEn 1200 mg 6%(6/95) and placebo 13% (12/95). The discontinuations due to adverse events in the GEn treatment groups appeared to be dose dependent.

Protocol Violations
Major protocol deviations were defined in the reporting and analysis plan (RAP) by the Applicant prior to unblinding the study. The major protocol deviations leading to exclusion from the Per Protocol population are summarized in Table 10.

Table 10: Summary of Major Protocol Deviations Leading to Exclusion from the Per Protocol Population (ITT Population, PXN 110748)

	Number (%) of Subjects				
	PBO N = 95	GEn 1200 mg N = 107	GEn 2400 mg N = 82	GEn 3600 mg N = 87	Total N = 371
Total number of subjects with at least one major protocol deviation	**16 (17)**	**17 (16)**	**13 (16)**	**16 (18)**	**62 (17)**
Prohibited Concomitant medication[1]	4 (4)	3 (3)	3 (4)	3 (3)	13 (4)
Investigational Product non-compliance[2]	7 (7)	9 (8)	4 (5)	9 (10)	29 (8)
Diary non-compliance[3]	11 (12)	11 (10)	6 (7)	11 (13)	39 (11)
Received treatment other than what they were randomized to receive	0	0	1 (1)	0	1 (<1)

Data Source: Table 1.9

1. While the study was ongoing, the medical monitor or designee reviewed the medications taken during the study while blinded to study treatment assignment to determine which should be considered protocol deviations.
2. Subjects who had <80% or >120% compliance with study medication over the entire treatment period.
3. Subjects who completed <4 evening diaries during the last week on maintenance treatment.

Source: Clinical Study Report Protocol PXN110748, p. 42

A total of 62 subjects had major protocol deviations. The rate of major protocol deviations appeared comparable in the different treatment groups.

One subject (000508) received treatment to which he was not randomized between Week 8 and Week 9. For the remainder of the study he took the appropriate randomized treatment medication. This subject was analyzed in the treatment group to which he was randomized.

No subjects were excluded from the Per Protocol population based on the following prespecified major protocol deviations:

- Violation of inclusion criteria #3: A documented medical diagnosis of PHN of at least three months duration prior to screening
- Violation of exclusion criteria #4: A baseline 24-hour average pain intensity score ≥4.0 based on an 11-point PI-NRS, where at least four assessments of the daily 24-hour pain intensity score must have been recorded during the seven-day Baseline Period

- Violation of exclusion criteria #1: Other chronic pain conditions not associated with PHN (an exception was allowed if the pain condition was located at a different region of the body and other conditions were met)
- Excessive rescue medication use (rescue medication was reviewed while the study was ongoing)

Expired Medication
During the course of the study, a total of 25 subjects took medication beyond the expiration date but no subject took medication that was greater than 15 days past the expiration date (Table 11). These subjects were not excluded from the Per Protocol population.

Table 11: Listing of Subjects who received expired Medisets

Subject Number	Treatment Group	Maximum Days Past the Mediset Labeled Expiration Date
006054	GEn 1200 mg	10
000708	GEn 1200 mg	9
001957	GEn 3600 mg	10
004956	GEn 3600 mg	1
000006	GEn 1200 mg	5
000007	GEn 2400 mg	4
000503	GEn 1200 mg	9
000505	Placebo	10
006454	GEn 2400 mg	6
006155	GEn 1200 mg	1
008061	GEn 1200 mg	9
008062	GEn 2400 mg	12
004052	GEn 2400 mg	1
002754	GEn 1200 mg	15
006658	GEn 3600 mg	4
003655	GEn 2400 mg	7
007556	GEn 1200 mg	6
007652	GEn 3600 mg	2
007771	GEn 3600 mg	2
008159	GEn 1200 mg	3
009856	GEn 1200 mg	7
000875	GEn 2400 mg	1
000988	GEn 1200 mg	12
000992	Placebo	1
008810	GEn 2400 mg	3

Source: Clinical Study Report Protocol PXN110748, p. 44

Treatment Blind Broken
The treatment blind was broken for one subject (006658) at week 9 who was randomized to GEn 3600 mg. The subject, a 76 year old man with a history of hypertension and type 2 diabetes mellitus, was diagnosed with atrial fibrillation on ECG at this visit and unblinded to start treatment. He was downtitrated and withdrawn from the study.

Demographics

The demographic characteristics of the subjects randomized to GEn were similar to those subjects randomized to placebo with respect to age, sex, race, and body mass index (Table 12). The pain scores were also similar between the GEn and placebo groups with the exception of the GEn 2400 mg treatment group having a lower mean baseline pain score than the other treatment groups.

Table 12: Summary of Demographic Characteristics

	PBO N = 95	GEn 1200 mg N = 107	GEn 2400 mg N = 82	GEn 3600 mg N = 87	Total N = 371
Age (y)					
Mean (SD)	61.7 (12.77)	61.7 (12.58)	64.1 (8.94)	61.3 (15.41)	62.1 (12.67)
Median	64.0	65.0	65.0	63.0	64.0
Range	18 – 83	18 – 87	21 – 83	20 – 92	18 - 92
Age Group, n (%)					
≤65 yrs	53 (56)	62 (58)	47 (57)	47 (54)	209 (56)
>65 yrs	42 (44)	45 (42)	35 (43)	40 (46)	162 (44)
Sex, n (%)					
Female	45 (47)	54 (50)	35 (43)	48 (55)	182 (49)
Male	50 (53)	53 (50)	47 (57)	39 (45)	189 (51)
Race, n (%)					
White[1]	79 (84)	94 (89)	69 (85)	73 (84)	315 (86)
BMI, n (%)					
≤30	57 (60)	62 (58)	46 (57)	56 (64)	221 (60)
>30	38 (40)	45 (42)	35 (43)	31 (36)	149 (40)
Baseline 24-hour average pain score, n (%)					
4 - <6.5	56 (59)	63 (59)	58 (71)	47 (54)	224 (60)
>6.5 - 10	39 (41)	44 (41)	24 (29)	40 (46)	147 (40)
Baseline 24-hour average pain score					
Mean (SD)	6.33 (1.370)	6.28 (1.525)	5.98 (1.569)	6.47 (1.579)	NA
Range	4.1 – 9.4	4.0 – 10	4.0 – 9.8	4.0 – 10.0	NA
Creatinine Clearance, est. (mL/min)					
Mean (SD)	96.2 (35.63)	94.4 (26.46)	91.2 (25.16)	90.3 (29.77)	NA
Range	39 – 290	52 – 182	49 – 180	34 – 177	NA

Source: Clinical Study Report, Protocol PXN110748, p. 46

Creatinine Clearance

The mean creatinine clearance (CrCl) was comparable across all treatment groups and ranged from 90.3 to 96.2 mL/min. There were 14 subjects enrolled with CrCl less than 60 mL/min, in violation of the protocol eligibility criteria (Table 13).

Table 13: Subjects Enrolled with Baseline CrCl<60 mL/min

Subject	Treatment Group
000318	GEn 3600 mg
000703	GEn 3600 mg
000856	GEn 3600 mg
004054	GEn 3600 mg
005754	PBO
006256	GEn 3600 mg
006355	GEn 2400 mg
007554	PBO
007753	GEn 1200 mg
007755	PBO
008807	GEn 3600 mg
008809	PBO
009859	GEn 3600 mg
009952	GEn 3600 mg

Source: Clinical Study Report, Protocol PXN110748, p. 47

Efficacy Results

Primary Endpoint:

The protocol-specified primary efficacy endpoint was the "change from baseline to end of treatment with respect to the mean 24-hour average pain intensity score based on an 11-point NRS." Table 14 presents treatment differences in the change in pain scores from Baseline to EOMT between GEn groups and placebo (PBO) using different imputation methods. The protocol-specified imputation method was LOCF. All three GEn doses were statistically better than placebo using LOCF and other more conservative imputation methods. Treatment differences ranged from 0.7 to 1.07 using the LOCF imputation method.

Efficacy Results Excluding Sites 048784 and (b) (4)

The primary efficacy analysis was rerun by the Applicant excluding data from two investigational sites. One of these sites (048784) was determined by their institutional review board (IRB) to be in serious non-compliance with federal regulations and the requirements of the board following an audit at the site. At the second site (b) (4) an investigator reported significant financial interest in GSK on the Financial Disclosure Form part B. Site 048784 enrolled 8 subjects and Site (b) (4) enrolled (b) (4) subjects in this study. When the Applicant recalculated the primary efficacy endpoint without those two treatment sites using the protocol-specified LOCF imputation method, the findings were still statistically significant (
Table **15**). The FDA statistician accepted the Applicant's reanalysis.

Table 14: Treatment Difference vs. PBO for Change from Baseline in Mean 24-Hour Average Pain Intensity Score at End of Maintenance Treatment with Different Imputation Methods for Study PXN110748

Imputation Method		GEn 1200 mg N = 107	GEn 2400 mg N = 82	GEn 3600 mg N = 87
ITT (LOCF)	N	106	80	87
	Adjusted Mean Difference vs. PBO[1]	-0.81	-0.70	-1.07
	95% CI	(-1.40, -0.23)	(-1.33, -0.07)	(-1.68, -0.45)
	p-value Adjusted for Multiplicity[2]	0.013	0.029	0.002
	Unadjusted p-value[3]	0.007	0.029	0.001
ITT (BOCF)	N	107	81	87
	Adjusted Mean Difference vs. PBO[1]	-0.94	-0.65	-0.68
	95% CI	(-1.51, -0.36)	(-1.27, -0.03)	(-1.28,-0.08)
	Unadjusted p-value[3]	0.001	0.040	0.027
ITT (BOCF/LOCF Hybrid)	N	107	81	87
	Adjusted Mean Difference vs. PBO[1]	-0.74	-0.51	-0.65
	95% CI	(-1.33,-0.15)	(-1.14, 0.13)	(-1.27, -0.03)
	Unadjusted p-value[3]	0.014	0.119	0.040
ITT (OC)	N	103	80	86
	Adjusted Mean Difference vs. PBO[1]	-0.86	-0.72	-1.08
	95% CI	(-1.45, -0.27)	(-1.35, -0.09)	(-1.70, -0.47)
	Unadjusted p-value[3]	0.004	0.025	0.001
Per Protocol (LOCF)	N	90	68	71
	Adjusted Mean Difference vs. PBO[1]	-0.99	-0.77	-1.25
	95% CI	(-1.59, -0.39)	(-1.42, -0.12)	(-1.89, -0.61)
	Unadjusted p-value[3]	0.001	0.020	<0.001
ITT, MMRM (OC)	N	103	81	86
	Adjusted Mean Difference vs. PBO[1]	-0.81	-0.68	-1.07
	95% CI	(-1.32, -0.31)	(-1.23, -0.14)	(-1.61, -0.54)
	Unadjusted p-value[3]	0.001	0.014	<0.001

Data Source: Table 2.3, Table 2.9. Table 2.13, Table 2.17, Table 2.20, Table 2.21

1. A negative treatment difference indicates benefit, relative to placebo.
2. Adjusted p-values are valid for inference of the LOCF ITT analysis only. Adjustments to p-values were made based on multiple treatment arms compared vs. placebo.
3. Unadjusted p-values are provided for descriptive purposes, and were not adjusted for multiple comparisons.

Source: Clinical Study Report, Protocol PXN110748, p. 51

Table 15: Change from Baseline in Mean 24-Hour Average Pain Intensity Score at End of Maintenance Treatment Excluding Data from Sites 048784 and (b) (4) (ITT, LOCF, PXN110748)

Imputation Method		GEn 1200 mg	GEn 2400 mg	GEn 3600 mg
ITT (LOCF)	n	103	78	84
	Adjusted Mean Difference vs. PBO[1]	-0.75	-0.67	-1.03
	95% CI	(-1.34, -0.15)	(-1.31, -0.02)	(-1.66, -0.40)
	Adjusted p-value[2]	0.028	0.043	0.004

Data Source: Table 2.106
1. A negative treatment difference indicates benefit, relative to placebo.
2. Adjustments to p-values were made based on multiple treatment arms compared vs. placebo.

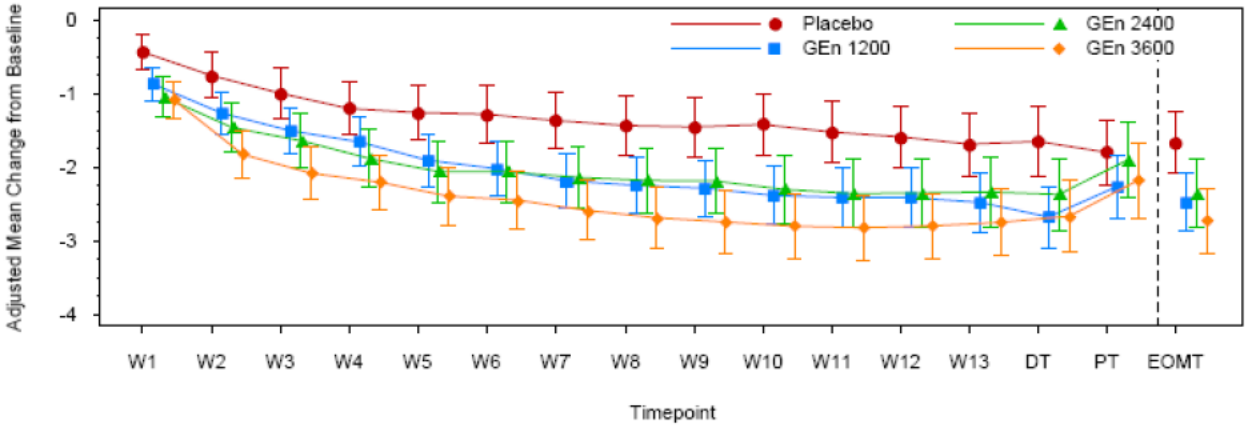
Source: Clinical Study Report, Protocol PXN110748, p. 52

Secondary Efficacy Endpoints

Change in Pain Intensity by Week

The change in mean 24-hour average pain intensity score from baseline to each week of treatment and post-treatment (including the End of Maintenance Treatment [EOMT]) in the ITT population (using LOCF data) is presented in Figure 2. A benefit over placebo was observed for all 3 doses of GEn as early as Week 1 and maintained across all timepoints.

Figure 2: Adjusted Mean (95% CI) Change From Baseline in 24-Hour Average Pain Intensity by Week and at the EOMT (ITT, LOCF, PXN110748)



Sample Size (n)

Placebo	95	95	95	95	95	95	95	95	95	95	95	95	95	73	82	95
GEn 1200	106	106	106	106	106	106	106	106	106	106	106	106	106	92	88	106
GEn 2400	80	80	80	80	80	80	80	80	80	80	80	80	80	67	63	80
GEn 3600	87	87	87	87	87	87	87	87	87	87	87	87	87	65	61	87

Source: Figure 2, Clinical Study Report, Protocol PXN110748, p. 53

Evening Pain Assessments
(Table 16) presents the adjusted mean change from baseline to EOMT for each treatment group and treatment differences vs. placebo for the following subject-reported evening pain assessments: day-time average pain, day-time worst pain and current evening pain. All three GEn treatment groups showed a greater reduction in pain than placebo with the exception for the GEn 2400 mg treatment group for day-time worst pain where the confidence interval did not suggest a difference from placebo. Confidence intervals were not adjusted for multiplicity.

Table 16: Change from Baseline at End of Maintenance Treatment and Treatment Differences (vs. PBO) in Subject-Reported Evening Pain Assessments (ITT, LOCF, PXN110748)

Percentage Reduction from Baseline	PBO N=95	GEn 1200 mg N=107	GEn 2400 mg N=82	GEn 3600 mg N=87
Day-time average pain				
n	95	106	80	87
Adj mean change	-1.59	-2.47	-2.23	-2.67
SE	0.22	0.21	0.24	0.23
Treatment difference	-	-0.88	-0.64	-1.08
95% CI	-	(-1.47, -0.29)	(-1.27, -0.00)	(-1.70, -0.46)
Day-time worst pain				
n	95	106	80	87
Adj mean change	-1.74	-2.61	-2.41	-2.82
SE	0.24	0.23	0.27	0.25
Treatment difference	-	-0.88	-0.68	-1.08
95% CI	-	(-1.53, -0.22)	(-1.38, 0.03)	(-1.77, -0.40)
Current evening pain				
n	95	106	80	87
Adj mean change	-1.45	-2.45	-2.24	-2.69
SE	0.23	0.21	0.25	0.24
Treatment difference	-	-1.00	-0.79	-1.24
95% CI	-	(-1.61, -0.39)	(-1.45, -0.14)	(-1.88, -0.60)

Data Source: Table 2.32, Table 2.41, Table 2.44
A negative treatment difference indicates benefit, relative to placebo.
Adjusted mean, SE and 95% CI are based on an ANCOVA model with BMI, baseline score, grouped center, and treatment as terms in the model.
Treatment difference: placebo versus active treatment groups.
Source: Table 16, Clinical Study Report, Protocol PXN110748, p. 54

Morning Pain Assessments

Table 17 presents the adjusted mean change from baseline to EOMT for each treatment group and treatment differences vs. placebo for the following subject-reported morning pain assessments: night-time average pain, night-time worst pain and current morning pain. All three GEn treatment groups showed a greater reduction in pain than placebo with confidence intervals not multiplicity-adjusted.

Table 17: Change from Baseline at End of Maintenance Treatment and Treatment Differences (vs. PBO) for Subject-Reported Morning Pain Assessments (ITT, LOCF, PXN110748)

Endpoint Assessment	PBO N=95	GEn 1200 mg N=107	GEn 2400 mg N=82	GEn 3600 mg N=87
Night-time average pain				
n	95	107	81	86
Adj mean change	-1.65	-2.35	-2.44	-2.50
SE	0.22	0.21	0.24	0.23
Treatment difference	-	-0.69	-0.78	-0.84
95% CI	-	(-1.28, -0.10)	(-1.42, -0.15)	(-1.47, -0.22)
Night-time worst pain				
n	95	107	81	86
Adj mean change	-1.76	-2.49	-2.65	-2.71
SE	0.24	0.23	0.26	0.25
Treatment difference	-	-0.73	-0.88	-0.94
95% CI	-	(-1.37, -0.08)	(-1.58, -0.19)	(-1.62, -0.26)
Current morning pain				
n	95	107	81	86
Adj mean change	-1.34	-2.29	-2.13	-2.41
SE	0.22	0.21	0.24	0.23
Treatment difference	-	-0.96	-0.79	-1.07
95% CI	-	(-1.56, -0.36)	(-1.44, -0.14)	(-1.71, -0.44)

Data Source: Table 2.35, Table 2.38, Table 2.47
A negative treatment difference indicates benefit, relative to placebo.
Adjusted mean, SE and 95% CI are based on an ANCOVA model with BMI, baseline score, grouped center, and treatment as terms in the model.
Treatment difference: placebo versus active treatment groups.

Source: Table 17, Clinical Study Report, Protocol PXN110748, p. 55

Responder Analysis
Table 18 prepared by the Applicant shows the proportion of subjects in the ITT population (using LOCF data) who achieved various responder criteria with respect to the mean 24-hour average pain intensity score at EOMT. A greater proportion of subjects were responders for all percent levels of pain reduction in the three GEn treatment groups compared to placebo. The GEn 3600 mg treatment group had the greatest number of responders for all percent reductions in baseline pain levels. The number of responders for GEn 1200 mg and GEn 2400 mg treatment groups appeared similar. The FDA statistician prepared a similar responder rate table using BOCF data (Table 21). Using this imputation method, the GEn 1200 mg treatment group had the greatest number of responders for 50% improvement from baseline in pain levels and appeared as effective as GEn 3600 mg.

Table 18: Responder Rates for 24-Hour Average Pain Intensity at the End of Maintenance Treatment (ITT, LOCF, PXN110748)

Endpoint Assessment	PBO N=95	GEn 1200 mg N=107	GEn 2400 mg N=82	GEn 3600 mg N=87
n	95	106	81	87
≥0	79 (83%)	94 (89%)	71 (88%)	84 (97%)
≥10%	62 (65%)	83 (78%)	61 (75%)	70 (80%)
≥20%	50 (53%)	71 (67%)	55 (68%)	65 (75%)
≥30%	40 (42%)	57 (54%)	48 (59%)	52 (60%)
≥40%	32 (34%)	50 (47%)	39 (48%)	46 (53%)
≥50%	22 (23%)	44 (42%)	28 (35%)	37 (43%)
≥60%	15 (16%)	34 (32%)	24 (30%)	31 (36%)
≥70%	9 (9%)	25 (24%)	18 (22%)	24 (28%)
≥80%	8 (8%)	17 (16%)	12 (15%)	19 (22%)
≥90%	3 (3%)	9 (8%)	9 (11%)	12 (14%)
100%	1 (1%)	6 (6%)	3 (4%)	7 (8%)

Source: Table 18, Clinical Study Report, Protocol PXN110748, p. 56

Rescue Medication Use
There was greater reduction in rescue medication use in all three GEn treatment groups compared to placebo with the greatest reduction occurring in the 1200 mg treatment group (Table 19). Rescue medication use was defined as the daily amount in milligrams of acetaminophen used for the ITT population (using LOCF data). There was no adjustment for multiplicity. The endpoint was calculated as the daily milligrams of acetaminophen averaged over the course of a week and was assessed in terms of the

adjusted mean change from baseline to EOMT in the average daily milligrams of acetaminophen used.

Table 19: Treatment Difference vs. PBO in Change from Baseline in Mean Daily Dosage of Rescue Medication (mg) at EOMT (ITT, LOCF, PXN110748)

Endpoint Assessment	PBO N=95	GEn 1200 mg N=107	GEn 2400 mg N=82	GEn 3600 mg N=87
N	95	106	80	87
Adj mean change	-41.00	-289.94	-260.03	-266.21
SE	89.49	84.35	97.85	93.50
Treatment difference	-	-248.93	-219.03	-225.20
95% CI	-	(-490.5, -7.33)	(-479.8, 41.77)	(-479.0, 28.60)

Data Source: Table 2.53
A negative treatment difference indicates benefit, relative to placebo.
Adjusted mean, SE and 95% CI are based on an ANCOVA model with BMI, baseline mean daily dose of rescue medication, and grouped center, and treatment as terms in the model.
Source: Table 21, Clinical Study Report, Protocol PXN110748, p. 60

Global Impression of Change
The Patient Global Impression of Change (PGIC) and the Clinician Global Impression of Change (CGIC) scales were used to determine the proportion of subjects who were responders using LOCF data. A responder was defined as any subject with a rating of 'much improved' or 'very much improved'.

For PGIC, the percentage of subjects who were responders was greater in the GEn 3600 mg (51%), GEn 2400 mg (45%) and GEn 1200 mg (44%) treatment groups as compared with the placebo treatment group (28%).

In the CGIC the percentage of subjects who were responders was greatest in the GEn 3600 mg (49%), GEn 2400 mg (50%) and GEn 1200 mg (45%) treatment groups as compared with placebo (31%).

Supportive Efficacy Studies

5.3.2 PXN110527

Study PXN110527 was a Phase 2a double-blind, 2-period, crossover study of GEn in PHN subjects who had a history of inadequate response (based on investigator judgment) to at least 1800 mg/day of gabapentin.

Title: The investigation of the efficacy and pharmacokinetics of GEn in subjects with neuropathic pain associated with post-herpetic neuralgia (PHN) who have had an inadequate response to gabapentin treatment.

Dates Conducted:
The study was initiated 14 March 2008 and competed 27 July 2009.

Objectives:
Primary objective was to investigate the difference between two doses of GEn (3600 mg/day versus 1200 mg/day) on pain intensity.

Secondary objectives were to characterize the effect of each of the two doses on symptoms of pain and pain intensity, physical function, safety and the systemic exposure of gabapentin during the baseline treatment of 1800 mg/day gabapentin and following 1200 mg/day and 3600 mg/day GEn.

Study Description: This multicenter, randomized, double-blind, two-period, crossover study compared the efficacy of a high dose (3600 mg/day) versus a low dose (1200 mg/day) of oral GEn in adult subjects with PHN. PHN was defined as pain persisting for ≥3 months after healing of the shingles rash. In addition, subjects were required to have a history of an inadequate response (based on investigator judgment) to gabapentin at a dose of at least 1800 mg/day. Subjects who showed no response, to previous treatment with either gabapentin (≥1800 mg/day) or pregabalin (150-300 mg/day) taken for at least 4 weeks were not eligible for participation in the trial.

Eligible subjects were enrolled in a two week baseline period, which included treatment with 1800 mg/day gabapentin, during which daily pain, evaluated using an 11-point pain intensity numerical rating scale was recorded in an electronic patient diary. Subjects who completed at least four evening diaries during the seven days prior to the day of the randomization visit and who had a mean 24-hour average pain intensity score of ≥4 were randomized to receive GEn (either 1200 mg/day or 3600 mg/day in a 1:1 ratio) for Treatment Period 1 (28 days). Following completion of Treatment Period 1, all subjects received a dose of 2400 mg/day for 4 days during the crossover period, followed by an alternate fixed dose (either 3600 mg/day or 1200 mg/day in a 1:1 ratio) for Treatment Period 2 (28 days).

Efficacy Assessments/Endpoints
Primary Endpoint: The primary endpoint was the change from baseline to the last week of each treatment period with respect to the mean 24-hour average pain intensity score based on an 11-point numerical rating scale. The mean score for the last week of treatment was the calculated mean of the daily scores (based on at least 4 assessments) for the 7 days prior to the last completed diary entry of the treatment period.

Secondary Endpoints: The following secondary endpoints were assessed:

- Night-time average pain intensity score
- Current pain intensity score recorded in the morning and evening
- Night-time worst pain intensity score
- Sleep interference score
- 24-hour average pain intensity score
- Day-time average pain intensity score
- Day-time worst pain intensity score

Pharmacokinetic/Pharmacodynamic Assessments

The change from baseline in the mean 24-hour average pain intensity score for the last week of each treatment period and the mean 24-hour average pain intensity score for the last week of each treatment period based on the 11-point NRS were both used as PD endpoints for the graphical PK/PD exploration. Steady-state average concentration was used as the independent variable for the PK/PD exploration.

Study Results

Subject Disposition

Of the 138 subjects entered in the baseline period, a total of 96 subjects successfully completed this period and were randomized into one of two treatment sequences. Three subjects withdrew from the study due to adverse events. All three subjects who withdrew were on the GEn 1200 mg dose; their adverse events are summarized below.

Subject #1504 was a 56 year old, white female who 27 days following initiation of treatment with GEn 1200 mg reported a 'worsening of depression'. Treatment with GEn was discontinued. Her depression was reported resolved after 26 days.

Subject #4014 was a 48 year old woman who 2 days following initiation of treatment with GEn 1200 mg reported 'increased postherpetic neuralgia pain'. The next day, the subject reported 'sweating', 'crankiness and irritability' and 'drowsiness'. The duration of all four adverse events was approximately 2 weeks prior to resolution.

Subject#1808 was a 58 year old man who 8 days following initiation of treatment with GEn 1200 mg in Treatment Period 2 reported epigastric pain. Study drug was discontinued and symptoms resolved in four days.

Efficacy Results

The primary endpoint, change from baseline in the mean 24-hour average pain intensity score for the last week of each treatment period, was according to the Applicant statistically significant (p=0.013) with an adjusted mean difference of -0.29 between the GEn 3600 mg and GEn 1200 mg treatments. The Applicant reports that the sensitivity analyses for the primary endpoint consistently had a treatment difference which was indicative of a benefit of GEn 3600 mg relative to GEn 1200 mg.

Safety Summary
Safety findings from Study PXN110527 are summarized in Section 7 of this review.

5.3.3 XP009

Study XP009 was a Phase 2a, randomized, double-blind, placebo-controlled, 2-week proof of concept study in PHN.

Title: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Safety and Efficacy of XP13512 in Patients with Postherpetic Neuralgia

Objectives:
Primary objective was to assess the efficacy of GEn versus placebo in reducing pain associated with PHN.

Secondary objectives were to: (1) assess the effects of GEn for improvement in sleep, quality of life, and mood; (2) assess gabapentin PK; (3) examine the relationship between gabapentin concentrations produced from GEn and treatment response; and (4) assess GEn safety and tolerability.

Study Description:
Eligible subjects entered into a 7-day baseline period followed by an 11-day, open-label Neurontin treatment period. The Neurontin dose was increased over 4 days to a final dose of 600 mg taken 3 times daily (1800 mg/day), which was maintained for an additional 7 days of treatment. At the end of the Neurontin treatment period, subjects were randomized to 1200 mg GEn or placebo given every 12 hours for 14 days. The primary efficacy endpoint was the change in mean weekly pain scores from baseline assessment to the final study week.

Study Results
Subject Disposition
Of the 115 subjects enrolled in the study, 102 were randomized to receive either GEn (n=48) or placebo (n=54). In the GEn group 45/48 (94%) completed the study and in the placebo group 47/54 (87%) completed the study. The reasons for withdrawal in the GEn group were 'subject withdrew consent' for one subject and 'protocol non-compliance' for two subjects. There were no adverse events reported as a reason for withdrawal in the GEn group. In the placebo group a total of seven subjects withdrew from the study: four subjects were for 'adverse event' and three subjects were for 'subject withdrew consent'.

Efficacy Results
With regards to the primary endpoint, the Applicant reported that the change from baseline in mean weekly pain score for the final week of treatment using LOCF data, GEn 2400 mg demonstrated a statistically significant improvement over placebo with an adjusted mean treatment difference of -0.75 (p=0.032). The adjusted mean change from baseline for the GEn treatment group was -2.02 while the placebo group reported an adjusted mean change from baseline of -1.27. The Applicant used the ITT population which contained only 47 subjects in the GEn group since one subject dropped out prior to receiving any dose of study medication.

Safety Results
Safety findings from Study XP009 are summarized in Section 7 of this review.

5.3.4

The Applicant has provided published literature describing two adequate and well-controlled studies used as part of the Neurontin registration program for PHN. These two studies are also described in the product label for Neurontin. The Applicant has included this literature as part of the 505(b)(2) NDA to supplement the existing GEn data and to provide corroborative evidence of the safety and effectiveness of gabapentin in the management of PHN. The two studies referred to in this review as the Rowbotham Study and Rice Study (authors of the papers), are summarized below.

Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA.* 1998;280(21):1837-42.

Objectives: To determine the efficacy and safety of gabapentin in reducing PHN pain

Design: Multicenter, randomized, double-blind, placebo-controlled, parallel design, 8-week trial

Intervention: A total of 229 subjects were randomized to either a 4-week titration period to a maximum dosage of 3600 mg/d of gabapentin or matching placebo followed by another 4 weeks of treatment at the maximum tolerated dose. Concomitant tricyclic antidepressants and/or narcotics were continued if therapy was stabilized prior to study entry and remained constant throughout the study.

Main Outcome Measures: The primary efficacy measure was change in the average daily pain score based on an 11-point Likert scale from baseline week to the final week of therapy. Secondary measures included average daily sleep scores, Short-Form McGill Pain Questionnaire (SF-MPQ), Subject Global Impression of Change and investigator-rated Clinical Global Impression of Change, Short Form-36 (SF-36) Quality of Life Questionnaire, and Profile of Mood States (POMS). Safety measures included the frequency and severity of adverse events.

Results: One hundred thirteen patients received gabapentin, and 89 (78.8%) completed the study; 116 received placebo, and 95 (81.9%) completed the study. By intent-to-treat analysis, subjects receiving gabapentin had a statistically significant reduction in average daily pain score from 6.3 to 4.2 points compared with a change from 6.5 to 6.0 points in subjects randomized to receive placebo (P<.001). Secondary measures of pain as well as changes in pain and sleep interference showed improvement with gabapentin (P<.001). Many measures within the SF-36 and POMS also significantly favored gabapentin (P≤.01). Somnolence, dizziness, ataxia, peripheral edema, and infection were all more frequent in the gabapentin group, but withdrawals were comparable in the 2 groups (15 [13.3%] in the gabapentin group vs. 11 [9.5%] in the placebo group).

Overall, the most frequently reported adverse effects among the gabapentin group, which occurred at higher incidences than those in the placebo group, were somnolence (27.4% vs. 5.2%), dizziness (23.9% vs. 5.2%), ataxia (7.1% vs. 0.0%), peripheral edema (9.7% vs. 3.4%), and infection (8.0% vs. 2.6%). Subjects in the older age range did not experience more of the central nervous system-related adverse effects of dizziness, somnolence, and ataxia than subjects in the younger age range.

A total of 15 (13.3%) and 11 (9.5%) of subjects in the gabapentin and placebo treatment groups, respectively, withdrew from the study for adverse events described as related to the study medication. Dizziness led to withdrawal from the study of 6 subjects (5.3%) treated with gabapentin, while somnolence led to the withdrawal of 5 subjects (4.4%) treated with gabapentin. In the placebo group, 2 subjects (1.7%) withdrew from the study because of somnolence, and there were no withdrawals because of dizziness.

Conclusions:
The authors concluded that in this 8-week study (4 weeks on maintenance dose), gabapentin was effective in the treatment of pain associated with PHN and also resulted in improvement in several secondary endpoints compared to placebo.

Rice ASC, Maton S. Gabapentin in postherpetic neuralgia a randomized, double blind, placebo controlled study. *Pain.* 2001;94:215-24.

Objectives: To evaluate the efficacy and safety of gabapentin 1800 or 2400 mg/day in treating PHN

Design: Multicenter, double blind, randomized, placebo controlled 7-week study

Intervention: A total of 334 men and women aged at least 18 years (mean 73) received gabapentin 1800 or 2400 mg daily or placebo in three divided doses with a forced titration schedule. There was a 4-day forced titration, during which the gabapentin dose was increased by 300 mg/day, over the first 4 days, up to 1200 mg/day. From days 4 to

7, dosing remained stable. After 1 week on treatment, the dose was titrated up to 1800 mg/day (1500 mg/day on day 8 and 1800 mg/day on days 9–14), and after 2 weeks, patients randomized to gabapentin 2400 mg/day had their dose titrated up to this final level (2100 mg/day on day 15 and 2400 mg/day from day 16 onwards). Patients who were unable to tolerate the dose regimen were withdrawn from the study. Patients remained on a stable dose from weeks 3 to 7.

Main Outcome Measures: The primary outcome measure was change in average daily pain score measured on an 11-point Likert scale from the baseline week to the final study week. Secondary outcomes included mean weekly sleep interference score; Short Form-McGill Pain Questionnaire (SF-MPQ); Clinician and Patient Global Impression of Change (CGIC/PGIC); Short Form-36 Health Survey (SF-36).

Results: From week 1, pain scores showed a significantly greater improvement with gabapentin: the final difference versus baseline was -34.5% for the 1800 mg dose, -34.4% for the 2400 mg dose compared with -15.7% for the placebo group. The difference vs. placebo was 18.8% for the 1800 mg dose (95% confidence interval 10.9–26.8%; $P < 0.01$) and 18.7% for the 2400 mg dose (10.7–26.7%; $P < 0.01$). Sleep interference diaries showed a similar pattern. There were significant differences in favor of gabapentin for number of patients reporting >50% reduction in their pain intensity, in the CGIC and PGIC.

Safety: Five non-fatal serious adverse events (SAEs) occurred during the study that were all considered by the authors to be unrelated to study drug. One SAE occurred in the placebo group (depression), three in the gabapentin 1800 mg group (fever, infection and retinal vein thrombosis and hemoptysis), and one in the gabapentin 2400 mg group (congestive heart failure). The most common adverse events were dizziness and somnolence, particularly during the titration phase. Dizziness and drowsiness were the most common adverse events necessitating withdrawal in the gabapentin groups; 7% of patients in each dose group withdrew because of dizziness and 5–6% because of drowsiness. The most frequently reported adverse effects among the gabapentin groups compared to placebo, were dizziness (placebo 9.9%, gabapentin 1800 mg 31%, gabapentin 2400 mg 33%), somnolence (placebo 6.3%, gabapentin 1800 mg 17.4%, gabapentin 2400 mg 20.4 %), peripheral edema (placebo 0%, gabapentin 1800 mg 5.2%, gabapentin 2400 mg 11.1%).

Conclusions:
The authors concluded that this 7-week study demonstrated gabapentin was effective in the treatment of pain associated with PHN and also resulted in improvement in several secondary endpoints.

Summary of two studies:
The Applicant submitted literature describing the two principal studies used to demonstrate efficacy in the Neurontin registration program for the treatment of PHN. Both randomized, double-blind, placebo-controlled studies showed statistically significant improvement in pain compared to placebo. However, additional benefit of using doses greater than 1800 mg/day of gabapentin was not demonstrated.

6 Review of Efficacy

Efficacy Summary

Efficacy of GEn in the management of PHN in adults was demonstrated in one principal efficacy study (PXN110748). There was statistically significantly less pain at 12 weeks in subjects treated with GEn compared to placebo. The finding of efficacy was supported by two additional Phase 2 studies (XP009 and PXN110527) and published literature demonstrating efficacy of the active drug, gapapentin, in two studies used in the Neurontin registration program. Studies XP009 and PXN110527 although considered supportive of the efficacy findings in PXN110748 were not considered adequate to support a finding of efficacy on their own due to their design (i.e., duration of two weeks or no placebo control). Therefore the efficacy findings from these studies were not reviewed by the FDA statistician.

Study PXN110748 was a placebo-controlled study that enrolled subjects with neuropathic pain associated with post-herpetic neuralgia. Eligible subjects were randomized to receive one of the following: GEn 3600 mg/day, GEn 2400/day, GEn 1200 mg/day or matching placebo. Efficacy was demonstrated with all three doses at 12 weeks. Additional benefit of using doses of greater than 1,200 mg a day was not demonstrated, and these higher doses were less well tolerated.

Issues
Last observation carried forward (LOCF) imputation was the prespecified method of imputation for missing data by the Applicant. The Division does not like this imputation method for analgesic studies since a good outcome score may be assigned to subjects who have a bad outcome (i.e., drop out due to an adverse event). However, the FDA statistician confirmed that the primary efficacy endpoint demonstrated efficacy with more conservative imputation methods.

6.1 Indication

Proposed Indication
GSK's proposed indication is the following:

> Horizant (gabapentin enacarbil) Extended-Release Tablets are indicated for the management of postherpetic neuralgia (PHN) in adults.

Approved Indication
GSK's approved indication is the following:

> Horizant (gabapentin enacarbil) Extended-Release Tablets are indicated for the treatment of moderate-to-severe primary restless leg syndrome (RLS) in adults. Horizant is not recommended for patients who are required to sleep during the daytime and remain awake at night

6.1.1 Methods

The Applicant has submitted one principal efficacy study to support a finding of efficacy for the indication of Horizant for the management of postherpetic neuralgia in adults. This study was an adequate and well-controlled (i.e., randomized, double-blind, placebo-controlled) study in subjects with pain associated with post-herpetic neuralgia. The primary efficacy measure and the pre-specified primary endpoint, "change from baseline to end of treatment with respect to the mean 24-hour average pain intensity score based on an 11-point NRS" meet the Division's standards.

6.1.2 Demographics

The overall demographic and baseline characteristics of the subjects randomized to GEn were similar to those subjects randomized to placebo with respect to age, sex, race, and body mass index (Table 12). The mean age for placebo (61.7 years) and for GEn treatment groups (range 61.3 to 64.1 years) were similar. The pain scores were also similar between the GEn and placebo groups with the exception of the GEn 2400 mg treatment group having a lower mean baseline pain score than the other treatment groups.

6.1.3 Subject Disposition

A total of 29% (80/281) of subjects in the GEn treatment groups and 33% (31/95) of subjects in the placebo treatment group prematurely discontinued study drug (Table 9). However, more subjects discontinued study from the GEn 3600 mg treatment group 38% (34/90) than from any other treatment group. The GEn 3600 mg treatment group had the most discontinuations due to adverse events 18% (16/90) compared to GEn 2400 mg 14% (12/84), GEn 1200 mg 6%(6/95) and placebo 13% (12/95).

Discontinuations due to adverse events in the GEn treatment groups appeared to be dose dependent.

6.1.4 Analysis of Primary Endpoint(s)

Choice of Primary Endpoint for PXN110748

The primary efficacy endpoint for Study PXN110748 was change from baseline to end of treatment with respect to the mean 24-hour average pain intensity score based on an 11-point NRS (0 = "no pain" and 10 = "pain as bad as you can imagine"). The 24-hour average pain intensity score was the subject's assessment of their average pain intensity over the preceding 24 hours. The mean baseline score was the calculated mean of the daily scores during the 7 days prior to randomization. The mean end of treatment score was the calculated mean of the daily scores during the last 7 days of the maintenance treatment. The Applicant's choice of primary endpoint is consistent with the Division's current standard.

Efficacy Results

Primary Endpoint:

The protocol-specified primary efficacy endpoint was the "change from baseline to end of treatment with respect to the mean 24-hour average pain intensity score based on an 11-point NRS." The protocol-specified imputation method was LOCF. Table 20 (same as Table 14) presents the change in pain scores from Baseline to End of Maintenance Treatment using different imputation methods. The FDA statistician confirmed the findings as reported by the Applicant for the first four imputation methods shown in the table but did not reanalyze the last two: PP subgroup and MMRM model. All three GEn doses were statistically better than placebo using LOCF and other more conservative imputation methods. Treatment differences ranged from 0.7 to 1.07 using the LOCF imputation method.

Table 20: Treatment Difference vs. PBO for Change from Baseline in Mean 24-Hour Average Pain Intensity Score at End of Maintenance Treatment with Different Imputation Methods for PXN110748

Imputation Method		GEn 1200 mg N = 107	GEn 2400 mg N = 82	GEn 3600 mg N = 87
ITT (LOCF)	N	106	80	87
	Adjusted Mean Difference vs. PBO[1]	-0.81	-0.70	-1.07
	95% CI	(-1.40, -0.23)	(-1.33, -0.07)	(-1.68, -0.45)
	p-value Adjusted for Multiplicity[2]	0.013	0.029	0.002
	Unadjusted p-value[3]	0.007	0.029	0.001
ITT (BOCF)	N	107	81	87
	Adjusted Mean Difference vs. PBO[1]	-0.94	-0.65	-0.68
	95% CI	(-1.51, -0.36)	(-1.27, -0.03)	(-1.28,-0.08)
	Unadjusted p-value[3]	0.001	0.040	0.027
ITT (BOCF/LOCF Hybrid)	N	107	81	87
	Adjusted Mean Difference vs. PBO[1]	-0.74	-0.51	-0.65
	95% CI	(-1.33,-0.15)	(-1.14, 0.13)	(-1.27, -0.03)
	Unadjusted p-value[3]	0.014	0.119	0.040
ITT (OC)	N	103	80	86
	Adjusted Mean Difference vs. PBO[1]	-0.86	-0.72	-1.08
	95% CI	(-1.45, -0.27)	(-1.35, -0.09)	(-1.70, -0.47)
	Unadjusted p-value[3]	0.004	0.025	0.001
Per Protocol (LOCF)	N	90	68	71
	Adjusted Mean Difference vs. PBO[1]	-0.99	-0.77	-1.25
	95% CI	(-1.59, -0.39)	(-1.42, -0.12)	(-1.89, -0.61)
	Unadjusted p-value[3]	0.001	0.020	<0.001
ITT, MMRM (OC)	N	103	81	86
	Adjusted Mean Difference vs. PBO[1]	-0.81	-0.68	-1.07
	95% CI	(-1.32, -0.31)	(-1.23, -0.14)	(-1.61, -0.54)
	Unadjusted p-value[3]	0.001	0.014	<0.001

Data Source: Table 2.3, Table 2.9. Table 2.13, Table 2.17, Table 2.20, Table 2.21

1. A negative treatment difference indicates benefit, relative to placebo.
2. Adjusted p-values are valid for inference of the LOCF ITT analysis only. Adjustments to p-values were made based on multiple treatment arms compared vs. placebo.
3. Unadjusted p-values are provided for descriptive purposes, and were not adjusted for multiple comparisons.

Source: Clinical Study Report, Protocol PXN110748, p. 51

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoints of GEn for the treatment of PHN were consistent with the efficacy findings of the primary endpoint.

Change in Pain Intensity by Week
The change in mean 24-hour average pain intensity score from baseline to each week of treatment and post-treatment in the ITT population (using LOCF data) is presented in Figure 2. A benefit over placebo was observed for all 3 doses of GEn as early as Week one and maintained across all timepoints.

Evening Pain Assessments
All three GEn treatment groups showed a greater reduction in pain than placebo for day-time average pain, day-time worst pain and current evening pain with the exception for the GEn 2400 mg treatment group for day-time worst pain where the confidence interval did not suggest a difference from placebo (Table 16). Confidence intervals were not adjusted for multiplicity.

Morning Pain Assessments
All three GEn treatment groups showed a greater reduction in pain than placebo for day-time average pain, day-time worst pain and current evening pain with confidence intervals not multiplicity-adjusted (Table 17).

Responder Analysis
Table 21 prepared by the FDA statistician shows the proportion of subjects in the ITT population (using BOCF data) who achieved various responder criteria with respect to the mean 24-hour average pain intensity score at end of maintenance treatment. The responder graph is shown in

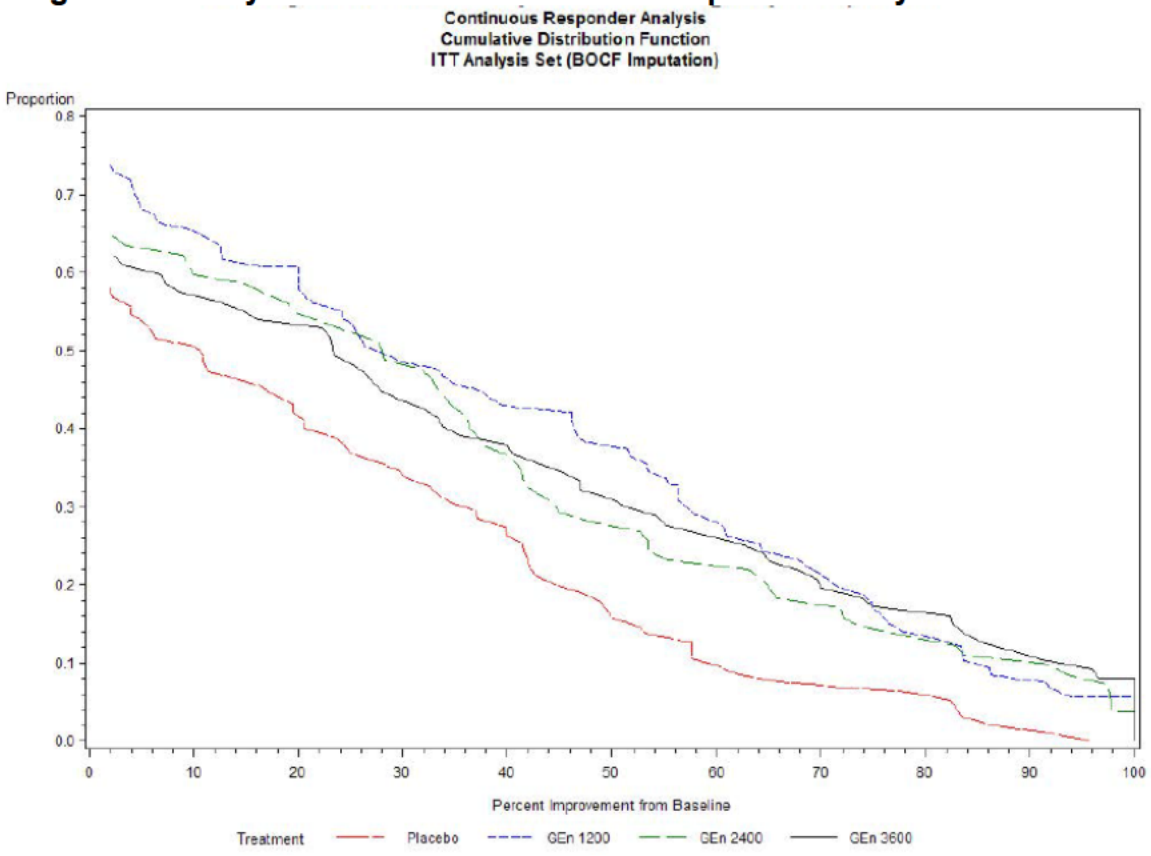
Figure 3. A greater proportion of subjects were responders for all percent levels of pain reduction in the three GEn treatment groups compared to placebo. The GEn 1200 mg treatment group had the greatest number of responders for 50% improvement from baseline in pain levels using the analysis prepared by the FDA statistician. In the Applicant's responder analysis using LOCF data, GEn 3600 mg treatment group had the greatest number of responders for all percent reductions in baseline pain levels (Table 18).

Table 21: Responder Analysis for Change in 24-Hour Average Pain Intensity from Baseline to EOMT (ITT, BOCF, PXN110748)

		Percent Improvement From Baseline									
Treatment Group	N	≥0% *	≥10%	≥20%	≥30%	≥40%	≥50%	≥60%	≥70%	≥80%	≥90%
Placebo	95	56 59%	48 51%	40 42%	33 35%	26 27%	16 17%	10 11%	7 7%	6 6%	2 2%
GEn 1200	107	80 75%	71 66%	65 61%	52 49%	46 43%	41 38%	31 29%	23 21%	15 14%	9 8%
GEn 2400	82	54 66%	50 61%	45 55%	40 49%	31 38%	23 28%	19 23%	15 18%	11 13%	9 11%
GEn 3600	87	55 63%	50 57%	47 54%	38 44%	34 39%	28 32%	23 26%	18 21%	15 17%	10 11%

*All subjects who discontinued prior to completing treatment for any reason were classified as non-responders.
Source: Katherine Meaker, MS, FDA Statistician

Figure 3: Study PXN 110748 Continuous Responder Analysis



Source: Katherine Meaker, MS, FDA Statistician

Rescue Medication Use
There was greater reduction in rescue medication use in all three GEn treatment groups, greatest in GEn 1200 mg, compared to placebo (Table 19). The change from baseline in mean daily dosage of rescue medication at end of maintenance was the following: -41 mg for PBO, -289 mg for GEn 1200 mg, -260 mg for GEn 2400 mg and -266 mg for GEn 3600 mg. Rescue medication use was defined as the daily amount in milligrams of acetaminophen used for the ITT population (using LOCF data). There was no adjustment for multiplicity. The endpoint was calculated as the daily milligrams of acetaminophen averaged over the course of a week and was assessed in terms of the adjusted mean change from baseline to end of maintenance treatment in the average daily milligrams of acetaminophen used. The FDA statistician confirmed the overall accuracy of the findings as reported by the Applicant.

Global Impression of Change
The PGIC and the CGIC scales were used to determine the proportion of subjects who were responders using LOCF data. A responder was defined as any subject with a rating of 'much improved' or 'very much improved'.
For PGIC, the percentage of subjects who were responders was greater in the GEn 3600 mg (51%), GEn 2400 mg (45%) and GEn 1200 mg (44%) treatment groups as compared with the placebo treatment group (28%). The FDA statistician confirmed the overall accuracy of the findings as reported by the Applicant.

In the CGIC the percentage of subjects who were responders was greatest in the GEn 3600 mg (49%), GEn 2400 mg (50%) and GEn 1200 mg (45%) treatment groups as compared with placebo (31%).

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The FDA statistician verified that the efficacy findings in Study PXN110748 were not significantly affected by age, sex or race. There were no clinically meaningful treatment-by-subgroup interactions.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There did not appear to be a clinically significant difference in efficacy between the doses of GEn studied.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy was demonstrated at the end of the 12 week maintenance phase.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In supporting the safety and tolerability of GEn in PHN, the Applicant presented in the Integrated Summary of Safety study data organized as follows:

- A brief summary of findings from the nonclinical studies relevant to human safety
- The 3 Phase 2 PHN clinical studies as follows:
  - 2 placebo-controlled PHN studies: principal 12-week PHN study (PXN110748) and supportive 2-week PHN study (XP009)
  - Supportive, 2-period crossover PHN study (PXN110527)
- 2 Phase 2 clinical studies in other pain indications as follows:
  - Study in neuropathic pain associated with diabetic peripheral neuropathy (DPN) (PXN110448) and the migraine headache prophylaxis study (MPX111381)
- The Phase 2/3 RLS clinical development program as follows:
  - 12-Week Placebo-Controlled Studies grouping (XP052, XP053, and XP081)
  - All RLS Studies grouping (XP052, XP053, XP081, XP083, XP060, XP021, XP045, and XP055),
  - RLS Long-Term Integration grouping (XP052, XP053, XP081, XP083 and XP055)
  - Phase 3b RLS-associated sleep disturbance study (RXP110908)
- The available data from Astellas studies as follows:
  - RLS Study 8825-CL-0003, RLS Study 8825-CL-0005, and DPN Study 825-CL-0007
- 17 Phase 1 studies are presented within the category of clinical pharmacology studies

The overall PHN clinical development program included 17 Phase 1 and the 3 Phase 2 PHN studies summarized in Table 3. Due to differences in study populations, designs, and durations, there was no integration of data across the PHN studies. However, the

Applicant did present data for each of the two placebo-controlled PHN studies in a side-by side format in the statistical displays. The Phase 1 studies were all previously submitted with the RLS NDA and reviewed during that submission.

7.1.2 Categorization of Adverse Events

Adverse Event (AE) data from all studies were reported in MedDRA version 13.1 only with the exception of data from PXN110527 (b) (4) Study PXN110527 was originally coded (for the purposes of the CSR) using MedDRA version 12.0. When the AEs reported during this study were recoded using MedDRA version 13.1, the Applicant reported that no coding differences were detected at the System Organ Class (SOC) or Preferred Term (PT) levels. (b) (4)

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As noted in section 7.1.1 there was not pooling of data across clinical trials due to differences in study populations, designs and durations of treatment.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The GEn development program provided adequate exposure to assess safety with a total of 2756 subjects exposed to at least one dose of GEn regardless of phase or indication and a total of 417 subjects exposed to GEn in Phase 2 PHN studies. The duration of exposure for principal Study PXN110748 is displayed in Table 22. This study provided the longest duration of exposures out of any of the PHN studies.

Table 22: Duration of Exposures by Mutually Exclusive Time Interval and Treatment Group (Study PXN110748)

Duration of Exposure[1]	Number (%) of Subjects				
	PBO (N=95)	GEn 1200 mg/day (N=107)	GEn 2400 mg/day (N=82)	GEn 3600 mg/day (N=87)	GEn All Doses (N=276)
≤7 days	4 (4)	3 (3)	3 (4)	6 (7)	12 (4)
>7 to ≤14 days	6 (6)	1 (<1)	4 (5)	4 (5)	9 (3)
>14 to ≤30 days	4 (4)	1 (<1)	6 (7)	6 (7)	13 (5)
>30 to ≤60 days	10 (11)	10 (9)	5 (6)	8 (9)	23 (8)
>60 to ≤90 days	7 (7)	4 (4)	2 (2)	7 (8)	13 (5)
>90 days	64 (67)	88 (82)	62 (76)	56 (64)	206 (75)

Data Source: PHN ISS, Table 1.6, PHN ISS, Table 1.8

GEn: gabapentin enacarbil; PBO: placebo

1. Represents the maximum length of exposure based on randomized treatment group for each subject including up-titration, maintenance and down-titration. The categories of duration are mutually exclusive. For this study, a duration of xx.5 was rounded up to the nearest whole number before categorizing, and vice versa. For example, a subject who had an exposure duration of 14.5 days was counted in the >14 to ≤30 days category while a subject with a duration of 14.2 days was counted in the >7 to ≤14 days category.

Reference: Table 20, ISS, p. 69

For Study (XP009), a 2 week study, a total of 47 subjects were exposed to GEn 2400 mg/day: 2 subjects for ≤ 7 days, 42 subjects for >7 to 14 days and 2 subjects for >14 to 30 days.

Study PXN110527 was a 2-period crossover study where subjects were treated with GEn 1200 mg/day and 3600 mg/day. Subjects also received a short duration of treatment with GEn 2400 mg/day during the titration period to 3600 mg/day. Exposures for this study are summarized in Table 23.

Table 23: Duration of Exposures to Each Dose of GEn by Mutually Exclusive Time Interval in Study PXN110527

Duration of Exposure in Days	GEn 1200 (N=91)	GEn 2400 (N=82)	GEn 3600 (N=85)
<=7 days	3 (3%)	78 (95%)	1 (1%)
>7-14 days	2 (2%)	3 (4%)	1 (1%)
>14-30 days	48 (53%)	1 (1%)	59 (69%)
>30-60 days	38 (42%)	0	24 (28%)

Source: Duration of Unique Subject Exposures Table, Integrated Summary of Safety, p. 293

7.2.2 Explorations for Dose Response

There was a dose-response relationship, with an increased incidence of AEs associated with higher GEn doses in principal Study PXN110748 (Table 24). Overall a total of 29% (80/281) of subjects in the GEn treatment groups and 33% (31/95) of subjects in the placebo treatment group prematurely discontinued study drug. However, more subjects

discontinued study from the GEn 3600 mg treatment group 38% (34/90) than from any other treatment group. The GEn 3600 mg treatment group had the most discontinuations due to adverse events 18% (16/90) compared to GEn 2400 mg 14% (12/84), GEn 1200 mg 6%(6/95) and placebo 13% (12/95).

Table 24: Summary of Subject Disposition and Primary Reasons for Premature Withdrawal (Study PXN110748)

	Number (%) of Subjects				
Completion Status	PBO (N=95)	GEn 1200 mg/day (N=107)	GEn 2400 mg/day (N=82)	GEn 3600 mg/day (N=87)	Total (N=371)
Completed	64 (67)	85 (79)	60 (73)	56 (64)	265 (71)
Withdrawn	31 (33)	22 (21)	22 (27)	31 (36)	106 (29)
Primary Reason for Withdrawal					
Adverse event	12 (13)	6 (6)	12 (15)	16 (18)	46 (12)
Withdrew consent	5 (5)	7 (7)	5 (6)	3 (3)	20 (5)
Protocol deviation	5 (5)	4 (4)	3 (4)	7 (8)	19 (5)
Lack of efficacy	6 (6)	1 (<1)	1 (1)	4 (5)	12 (3)
Investigator discretion	2 (2)	2 (2)	1 (1)	0	5 (1)
Lost to follow-up	1 (1)	2 (2)	0	1 (1)	4 (1)

Data Source: PHN ISS, Table 1.1
GEn: gabapentin enacarbil; PBO: placebo
Note: Reasons for withdrawal are ordered by decreasing incidence in the Total group.
Note: Subjects could have only one primary reason for withdrawal.
Source: Table 9 Integrated Summary of Safety, p. 55

No conclusion regarding a dose-response relationship could be made with respect to Study XP009 since only one dose (2400 mg/day) was studied. The overall discontinuation rate for that study due to an adverse event was 7% (4/54 subjects). Also no conclusion regarding a dose-response relationship could be made with respect to Study PXN110527 since withdrawal due to adverse events was comparable for the GEn 1200 to 3600 mg/day sequence and GEn 3600 to 1200 mg/day sequence.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the development of GEn appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to Section 4.4 and the Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The antiepileptic class of drugs have been associated with suicidal behavior and ideation and contain a class warning for suicide in the label.

7.3 Major Safety Results

7.3.1 Deaths

As of the 31 January 2011 cut-off date, there have been a total of six deaths among all 2756 subjects exposed to GEn, but no deaths among the 566 subjects in the Phase 2 PHN studies. The six deaths occurred as follows: 2 deaths (bronchopneumonia and accidental overdose) in the migraine headache prophylaxis study, 2 deaths (asphyxia and fall) reported in the Phase 2/3 RLS, 1 death (lymphoma) in the Astellas-sponsored studies, and 1 death (completed suicide) in a single-dose clinical pharmacology study.

Individual Patient Death Summaries

Subject 000526 (Protocol MPX111381)
Serious Events: Death, Bronchopneumonia

Subject 000526 was a 42-year-old woman enrolled in a blinded study for the treatment of migraine. She was found dead in her bedroom, 132 days after starting GEn. She had been randomized to 1800 mg/day dose but at the time of death was at Day 13 of taper and would have been at 1200 mg/day.

Her past medical history is significant for gastroesophageal reflux disease and low back pain due to a history of a herniated disc. Medications included Prilosec for gastro esophageal reflux and Aleve. She was treated with amoxicillin approximately two weeks prior to her death for bronchitis.

Post-mortem blood toxicology was positive for: Acetaminophen 4.8 mg/L (therapeutic range:10-20 mg/L), Cocaine metabolites, Oxycodone 0.367 mg/L, Alprazolam 0.368 mg/L, Carisoprodol 0.70 mcg/ml (therapeutic blood levels up to 25 mcg/ml and meprobamate 4.9 mcg/ml (therapeutic range: 10-30 mcg/ml), Citalopram 30 ng/ml (therapeutic range: 9-200 ng/ml), Clonazepam 7.3 ng/ml (therapeutic range: 10-75 ng/ml) and 7-amino clonazepam 170 ng/ml (therapeutic range 20-140 ng/ml), Mirtazapine 5.4 ng/ml (therapeutic range: 27-225 ng/ml peak; 4.3-64 ng/ml trough). At screening and throughout the duration of the trial she denied use of any restricted medications.

The autopsy report contained the following significant findings: Bronchopneumonia, dilated bladder, nasal septum perforation, and right pleural effusion. According to the

medical examiner the cause of death was bronchopneumonia due to drug use, manner of death was accidental.

Impression
The cause of death for this subject was bronchopneumonia related to drug abuse. There is no evidence that the cause of death was related to GEn.

Subject 10801 (Protocol MPX111381)
Serious Events: Death, Overdose

Subject 060516 was a 31-year-old male subject enrolled in a study for the prophylactic treatment of migraine headaches. The subject was randomized to GEn 2400 mg/day. Pertinent medical history includes alcohol and prescription drug abuse according to his wife. The subject died due to a drug overdose129 days after the start of investigational product. The subject was found lying next to a card table on which were the following items: a travel bag containing several prescription bottles containing marijuana, oxycodone, and alprazolam; a bong and marijuana grinder; and an empty beer can. There was an open 18 pack of beer in the refrigerator and several empty liquor bottles in the kitchen trash can. The oxycodone prescription was filled one day prior to his death for 60 15 mg pills; 54 pills remained in the bottle. The alprazolam was filled two days prior to his death for 30 0.5 mg pills; there were 6 pills remaining. His wife had spoken to him the day before he was found dead and described him as sounding intoxicated.

Impression
The cause of death for this subject was drug overdose due to oxycodone and alprazolam. There is no evidence that the death was related to GEn.

Subject 1864008 (Protocol XP060)
Serious Events: Death, Asphyxia

Subject 1864008 was a 63-year-old woman receiving GEn 1200 mg daily in a study for the treatment of RLS. The subject experienced aspiration of a piece of meat, 162 days after the start of investigational product. Attempts at resuscitation were unsuccessful.

Impression
The cause of death for this subject was asphyxia secondary to aspirating food. There is no evidence that the death was related to GEn.

Subject 1813027 (Protocol XP055)
Serious Events: Death, Fall

This 48-year-old man was enrolled in an open-label extension study for the treatment of RLS. He received GEn 1200 mg for approximately one year. Approximately 25 days

after the last dose of GEn, the subject fell from a highway overpass resulting in his death. Acute alcohol intoxication was listed as a significant condition on the death certificate. His mother stated that he never appeared depressed or expressed suicidal ideation and she did not feel this was suicide. She reported the subject had been drinking alcohol more and had been smoking marijuana.

Impression
The cause of death for this subject was a fall that was probably related to acute alcohol intoxication. There is no evidence that GEn contributed to his fall given that he had been off study drug for over three weeks.

Subject CL05-207-38 (Protocol 8825-CL-0005)
Serious Events: Death, Lymphoma

The subject was a 57 year old man enrolled in Astellas open-label study conducted in Japan for long term administration of GEn for the treatment of RLS. The subject was hospitalized 171 days after starting GEn for suspected malignant lymphoma with symptoms of “physical deconditioning” and fever. The subject died approximately one week later died (limited information provided). The autopsy showed findings of systemic metastasis of the malignant lymphoma.

Summary
The cause of death for this subject was malignant lymphoma. There is no evidence to suggest that the lymphoma was related to use of GEn.

Subject 044222 (Protocol XP044)
Serious Events: Death, Completed suicide

This 51-year-old man was enrolled in an open-label clinical pharmacology study in healthy adult subjects. He received a single dose of GEn 1200 mg under fed conditions and one week later received a single 1200 mg dose under fasting conditions. Following discharge from the study 36 hours after receiving the second dose, the subject was reported to have consumed a beer with dinner and then a "couple more beers" at a tavern. At around midnight following discharge from the study, nine days after the first dose of GEn and two days after the second dose, the subject committed suicide as a result of a gun shot wound to the head following a domestic dispute. Toxicology screen showed a blood ethanol level of 0.17 g/100mL (legal limit less than 0.08); the toxicology screen was negative for opiates, cocaine, amphetamines, PCP, marijuana, methadone, propoxyphene, benzodiazepines, barbiturates and tricyclic antidepressants. The subject's gabapentin level was below the limit of detection (less than 2 mg/L) at the time of autopsy. The subject's family history included suicide and manic depression. The subject did not report a history of substance abuse, bipolar or unipolar depression, or other psychiatric diagnosis but did have a history of alcohol use (12-14 beers per week).

Impression
The cause of death for this subject was suicide. It appears unlikely that GEn contributed to his suicide since he had received only two doses total with the first dose administered over one week prior to his suicide. Furthermore, he was acutely intoxicated at the time of the suicide and was reported to have a family history of suicide. However, since suicide has been reported with antiepileptic drugs it is impossible to completely exclude GEn as a contributing factor.

Overall Summary of Deaths
The deaths of all six subjects on GEn were reviewed. There were no deaths in the PHN development program. All the deaths appeared unrelated to GEn with the possible exception of one suicide. Since suicide is listed as a potential risk in patients on antiepileptic drugs, GEn cannot be completely excluded as a contributing cause. However, the case involving suicide could be explained by the subject's acute intoxication and other factors.

7.3.2 Nonfatal Serious Adverse Events

In the GEn development program for PHN, 11 subjects reported a total of 15 nonfatal SAEs during treatment and post-treatment. Two of the subjects with SAEs were treated with placebo. Three SAEs occurred post-treatment in 3 subjects and one subject (PXN110527/1504) was reported to have an SAE both during treatment and post-treatment. In the principal study PXN110748, nine subjects had 12 SAEs with one subject (PXN110748/4264) having a SAE of 'coronary artery disease' post-treatment (Table 25). Two subjects experienced nonfatal SAEs in PXN110527. There were no SAEs during treatment or post-treatment in study XP009.

The narratives of all subjects with SAEs on GEn in the PHN development program were reviewed. There is no clear evidence that any of the SAEs were related to study drug. Summaries of the SAEs for all nine subjects follow; summaries of the SAEs for the two subjects on placebo are not included in this review.

Table 25: Summary of Serious Adverse Events in Study PXN110748

System Organ Class Preferred Term	PXN110748			
	Placebo (N=95)	GEn 1200 (n=107)	GEn 2400 (N=82)	GEn 3600 (N=87)
Number of subjects any event	2 (2%)	1 (1%)	4 (5%)	2 (2%)
Nervous System Disorders	0	0	2 (2%)	0
Intracranial aneurysm	0	0	1 (1%)	0
Multiple sclerosis	0	0	1 (1%)	0
Multiple sclerosis relapse	0	0	1 (1%)	0
Gastrointestinal disorders	0	0	0	1 (1%)
Gastritis	0	0	0	1 (1%)
General disorders and administration site conditions	0	0	1 (1%)	0
Chest pain (non cardiac)	0	0	1 (1%)	0
Infections and infestations	0	0	1 (1%)	0
Sinusitis	0	0	1 (1%)	0
Investigations	0	0	1 (1%)	0
Blood pressure increased	0	0	1 (1%)	0
Psychiatric disorders	0	0	1 (1%)	0
Anxiety	0	0	1 (1%)	0
Reproductive system and breast disorders	0	0	0	1 (1%)
Cystocele	0	0	0	1 (1%)
Cardiac disorders	1 (1%)	0	0	0
Atrial fibrillation	1 (1%)	0	0	0
Coronary artery disease[1]		1 (1%)		
Injury, poisoning and procedural complications	1 (1%)	0	0	0
Vascular injury	1 (1%)	0	0	0

[1] SAE occurred post-treatment: Subject hospitalized 9 days after last dose of GEn for coronary artery disease and CABG

Individual Nonfatal Serious Adverse Event Summaries

Subject 875 (Protocol PXN110748)
Nonfatal Serious Adverse Event: Intracranial aneurysm

This 65 year old woman had an SAE of recurrent basilar artery aneurysm 65 days after the start of GEn. The subject underwent endovascular treatment.

Impression
There is no reasonable possibility that the recurrent basilar artery aneurysm was caused by GEn.

Subject 1355 (Protocol PXN110748)
Nonfatal Serious Adverse Event: Blood pressure increased

This 57 year old woman with a history of hypertension and type 2 diabetes was randomized to GEn 2400 mg starting 27 January 2009. On 03 February 2009, seven days after the starting GEn, an SAE of severe elevated blood pressure was reported. At her next study visit on 10 February 2009, the subject reported that she went to the cardiologist on (b) (6) with complaints of exhaustion, light-headedness, left arm numbness and upper back pain. The subject reports that BP on that day was 200/107 mmHg and ECG was normal. The subject was hospitalized. Treatment with GEn was continued. The event resolved on (b) (6) and the subject was discharged from hospital that same day. The subject also reported that she had undergone a stress test on 09 February 2009 and that the results were normal. The subject's BP on 17 February 2009 was 144/78 mmHg.

Impression
The elevated blood pressure does not appear to be related to GEn especially considering the event resolved while still on study drug.

Subject 1769 (Protocol PXN110748)
Nonfatal Serious Adverse Event: Coronary artery disease

This 72 year old man randomized to GEn 1200 mg received the drug from 31 December 2008 to 30 March 2009. The subject had an episode of angina diagnosed on 01 February 2009 and on 26 March 2009. Relevant concomitant medications included plavix, metoprolol, and aspirin. On (b) (6) days after the last dose), (b) (6) days after the starting GEn, the subject was diagnosed with severe coronary artery disease and was hospitalized. The subject had cardiac catheterization and underwent coronary artery bypass graft surgery that same day.

Impression
This subject's coronary artery disease does not appear to be related to GEn.

Subject 4264 (Protocol PXN110748)
Nonfatal Serious Adverse Event: Anxiety, Chest pain

This 73 year old woman randomized to GEn 2400 mg was reported to have developed severe atypical chest pain (non cardiac) and acute anxiety the same day the first dose of study drug was given. The subject had hypotension 82/52 mmHg. Cardiac enzymes were normal. The subject was hospitalized. Treatment with GEn was discontinued after the first dose. The subject was treated with nitroglycerine, aspirin, triazolam and lorazepam and was given oxygen. The atypical chest pain resolved after approximately two days and the acute anxiety resolved after approximately two weeks.

Impression
This subject's atypical chest pain does not appear to be directly related to study drug. GEn cannot be completely excluded as a cause of her anxiety; however the persistence of her anxiety for two weeks after a single dose of GEn would appear to make this an unlikely cause.

Subject 6051 (Protocol PXN110748)
Nonfatal Serious Adverse Events: Multiple sclerosis, Multiple sclerosis relapse, Sinusitis

This 60 year old woman randomized to GEn 2400 mg started receiving drug on 28 August 2008. The subject's medical history included advanced multiple sclerosis and chronic pain syndrome. On (b) (6) days after the start of GEn, she presented with severe multiple sclerosis and severe sinusitis. The subject was hospitalized. The subject reported headache, nausea, ataxia, weakness, leg pain and fatigue. A CT scan of the head on (b) (6) showed mild atrophy and near total opacification of the left maxillary sinus. A magnetic resonance imaging scan of the brain on (b) (6) showed findings compatible with advanced multiple sclerosis with atrophy and chronic opacification of the left maxillary sinus. The subject continued GEn in the hospital. The events resolved on (b) (6) and the subject was discharged in stable condition with improved ambulation. On discharge, the subject was given levofloxacin 500 mg po for 10 days and morphine IR 15 mg po every 4 hours prn. On (b) (6) days after the start of investigational product, an SAE of moderate exacerbation of multiple sclerosis was reported for this subject. The subject was again hospitalized. Treatment with investigational product was discontinued on (b) (6) and the subject was withdrawn from the study. The event resolved on (b) (6).

Impression
It is highly unlikely that GEn was responsible for her multiple sclerosis relapse or sinus infection.

Subject 7557 (Protocol PXN110748)
Nonfatal Serious Adverse Event:Cystocele

This 61 year old woman randomized to GEn 3600 mg started treatment 10 October 2008. On (b) (6) days after the starting GEn, she developed moderate stress incontinence due to third degree cystocele. The subject was hospitalized and underwent surgical repair of the cystocele. Treatment with investigational product was continued.

Impression
There is no reasonable possibility that the cystocele is related to the GEn.

Subject 2652 (Protocol PXN110748)
Nonfatal Serious Adverse Event: Gastritis

This 73 year old woman randomized to GEn 3600 mg developed severe gastritis 72 days after starting the study drug. She reported nausea, vomiting and abdominal pain. Her GEn was discontinued. The subject was hospitalized. Endoscopy showed gastritis and colonoscopy showed a 1.2 cm polyp fulgurated (colon biopsies were negative). The event was reported resolved four days after onset.

Impression
The investigator considered that there was a reasonable possibility that the gastritis may have been caused by investigational product. This reviewer considers that a causal relationship is possible but not definite given the temporal relationship of symptoms starting 72 days after treatment.

Subject 1504 (Protocol PXN110527)
Nonfatal Serious Adverse Events: Depression, Hallucination (auditory)

This 56 year old woman with a history of depression was randomized to receive GEn 1200 mg/day during period 1 and 3600 mg/day during period 2. Twenty six days after the start of investigational product, the subject developed severe worsened depression (considered by the investigator to be a non serious drug related AE). The subject was recommended for early termination and withdrew from the study on 26 March 2009. The subject entered the down titration phase on 26 March 2009 to 09 April 2009. Around this same time however, she decided she was unhappy with care by her current psychiatrist, so she changed doctors. The new psychiatrist put her on sertraline hydrochloride and amitriptyline starting 31 March 2009. At the post treatment visit on 09 April 2009, the subject said that the depression had not resolved and that she had an onset of auditory hallucinations on 31 March 2009. The depression and auditory hallucinations were so severe that on (b) (6) she was admitted to an inpatient mental health facility. The subject was discharged on (b) (6) and was much better.

Impression
The subject's auditory hallucinations and worsened depression requiring hospitalization were possibly related to starting sertraline and amitriptyline and less likely due to GEn which was being tapered at the time her symptoms started and had been discontinued at the time of her hospitalization. However, GEn cannot be excluded as a cause of her initial worsening of depression which was the reason for her discontinuing from the study.

Subject 3207 (Protocol PXN110527)
Nonfatal Serious Adverse Events: Chest pain

This 65 year old woman, 82 days after the start of investigational product and 12 days after the last dose, developed severe chest pain. The subject was hospitalized. On admission she was noted to have very high blood pressure. During her hospitalization no cause for her chest pain was identified.

Impression
GEn is unlikely to be the cause of this subject's chest pain occurring 12 days after her last dose of medication.

***PXN110527** Serious Adverse Events*
Two subjects experienced non-fatal SAEs.

Study XP009
One patient was hospitalized for pancreatitis during the screening period but before receiving any study medication. There were no SAEs after subjects received study drug.

7.3.3 Dropouts and/or Discontinuations

In the PHN development program dropouts in the three Phase 2 studies were 29% of the 371 subjects in PXN110748; 9% of the 101 subjects in XP009; and 19% of the 94 subjects in PXN110527. The incidence of premature withdrawals was increased with increasing doses of GEn in PXN110748 (21%, 27% and 36% at GEn 1200, 2400 and 3600 mg/day, respectively). However for the 1200 and 2400 mg/day doses the number of dropouts was less relative to placebo (33%) and in XP009, the incidence of premature withdrawals was substantially higher with placebo (13%) relative to GEn 2400 mg/day (4%).

Dropouts Due to Adverse Events
In Study PXN110748 dropouts due to adverse events were dose-related for GEn 1200, 2400 and 3600 mg/day at 6%, 15% and 18% respectively (Table 26). However,

dropouts due to adverse events occurred more often in placebo (13%) than in the GEn 1200 mg/day group (6%). Table 27 summarizes the most frequent adverse events leading to withdrawal.

Dropouts Other Studies

In Study *XP009*, a placebo-controlled 2-Week PHN study, subjects who prematurely withdrew due to an adverse event was higher with placebo 7% (4/54) relative to GEn 2400 mg/day 0% (0/47).

In Study PXN110527, the 2-period crossover PHN study the proportion of subjects who withdrew prematurely due to adverse events was comparable for the GEn 1200 to 3600 mg/day sequence 4% (2/50) and GEn 3600 to 1200 mg/day sequence 2% (1/44).

Table 26: Summary of Subject Disposition and Primary Reasons for Premature Withdrawal (Study PXN110748)

	Number (%) of Subjects				
Completion Status	PBO (N=95)	GEn 1200 mg/day (N=107)	GEn 2400 mg/day (N=82)	GEn 3600 mg/day (N=87)	Total (N=371)
Completed	64 (67)	85 (79)	60 (73)	56 (64)	265 (71)
Withdrawn	31 (33)	22 (21)	22 (27)	31 (36)	106 (29)
Primary Reason for Withdrawal					
Adverse event	12 (13)	6 (6)	12 (15)	16 (18)	46 (12)
Withdrew consent	5 (5)	7 (7)	5 (6)	3 (3)	20 (5)
Protocol deviation	5 (5)	4 (4)	3 (4)	7 (8)	19 (5)
Lack of efficacy	6 (6)	1 (<1)	1 (1)	4 (5)	12 (3)
Investigator discretion	2 (2)	2 (2)	1 (1)	0	5 (1)
Lost to follow-up	1 (1)	2 (2)	0	1 (1)	4 (1)

Data Source: PHN ISS, Table 1.1
GEn: gabapentin enacarbil; PBO: placebo
Note: Reasons for withdrawal are ordered by decreasing incidence in the Total group.
Note: Subjects could have only one primary reason for withdrawal.
Source: Integrated Summary of Safety, p. 55

Table 27: Adverse Events Leading to Withdrawal (at least 2%) in Any GEn Treatment Group in Study PXN110748

	Number (%) of Subjects			
	PBO (N=95)	GEn 1200 mg/day (N=107)	GEn 2400 mg/day (N=82)	GEn 3600 mg/day (N=87)
Any event	**12 (13)**	**6 (6)**	**12 (15)**	**16 (18)**
Preferred Term				
Dizziness	3 (3)	2 (2)	3 (4)	1 (1)
Somnolence	2 (2)	1 (<1)	1 (1)	3 (3)
Headache	0	0	2 (2)	0
Nausea	0	2 (2)	0	2 (2)
Fatigue	0	3 (3)	0	1 (1)
Edema peripheral	0	0	2 (2)	0

Source: Integrated Summary of Safety, p. 154

7.3.4 Significant Adverse Events

Discussed in section 7.3.2

7.3.5 Submission Specific Primary Safety Concerns

Not applicable.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events in GEn-treated subjects from Study PXN110748 are listed in Table 28. Dose-related incidences were observed for the two most common adverse events dizziness (15%, 17%, 26% and 30% for placebo, GEn 1200, 2400 and 3600 mg/day, respectively) and somnolence (8%, 10%, 11%, and 14% for placebo, GEn 1200, 2400 and 3600 mg/day, respectively). Peripheral edema also related to study drug had an incidence of 6% to 7% in the GEn groups compared to an incidence of 0% in the placebo group. Dose-related incidences were also observed for fatigue, insomnia and weight increased.

Reviewer's Note: For the RLS NDA the Applicant tabulated the most commonly observed adverse reactions by greater than 5% and at least two times the rate of placebo. This method for identifying adverse reactions in the PHN study would not yield meaningful results since the placebo rate of adverse events was relatively high and twice that rate would yield no cases.

Table 28: Most Common Adverse Events (incidence of at least 5% at Preferred Term Level in Any GEn Group in Study PXN110748

	Number (%) of Subjects				
	PBO (N=95)	GEn 1200 mg/day (N=107)	GEn 2400 mg/day (N=82)	GEn 3600 mg/day (N=87)	All GEn Doses (N=276)
Any Event	63 (66)	75 (70)	64 (78)	71 (82)	210 (76)
Preferred Term					
Dizziness	14 (15)	18 (17)	21 (26)	26 (30)	65 (24)
Somnolence	8 (8)	11 (10)	9 (11)	12 (14)	32 (12)
Headache	9 (9)	11 (10)	8 (10)	6 (7)	25 (9)
Nausea	5 (5)	9 (8)	3 (4)	8 (9)	20 (7)
Fatigue	1 (1)	5 (5)	4 (5)	9 (10)	18 (7)
Edema peripheral	0	6 (6)	6 (7)	5 (6)	17 (6)
Constipation	5 (5)	7 (7)	4 (5)	4 (5)	15 (5)
Diarrhea	5 (5)	6 (6)	2 (2)	6 (7)	14 (5)
Arthralgia	3 (3)	6 (6)	4 (5)	3 (3)	13 (5)
Insomnia	2 (2)	3 (3)	4 (5)	6 (7)	13 (5)
Nasopharyngitis	5 (5)	5 (5)	3 (4)	5 (6)	13 (5)
Urinary Tract Infection	3 (3)	8 (7)	2 (2)	1 (1)	11 (4)
Weight Increased	1 (1)	3 (3)	4 (5)	4 (5)	11 (4)
Back Pain	3 (3)	4 (4)	4 (5)	2 (2)	10 (4)
Dry Mouth	2 (2)	1 (<1)	4 (5)	4 (5)	9 (3)
Hypertension	1 (1)	2 (2)	4 (5)	2 (2)	8 (3)
Vision blurred	0	2 (2)	4 (5)	2 (2)	8 (3)
Nasal congestion	1 (1)	2 (2)	0	5 (6)	7 (3)
Flatulence	0	1 (<1)	1 (1)	4 (5)	6 (2)
Joint sprain	0	2 (2)	0	4 (5)	6 (2)
Tremor	0	0	0	4 (5)	4 (1)

Source: Summary Document Analysis Plan for Gabapentin Enacarbil PHN, Integrated Summary of Safety p. 33

For Study XP009 the common adverse events were reviewed and found to be similar to Study PXN110748. The most common adverse event was dizziness (21% GEn and 6% placebo).

Somnolence

GEn can cause somnolence but at the 1200 mg dose per day only 10% of patients reported somnolence compared with 8% of patients receiving placebo. Somnolence may be of greater concern in patients with RLS who already have impaired sleep and may suffer from daytime sleepiness.

7.4.2 Laboratory Findings

Clinical laboratory tests were performed in all three Phase 2 PHN studies. Due to the differences in study populations, designs, and durations, there was no integration of data across the PHN studies. For the principal efficacy study (PXN110748) the Applicant analyzed the hematology parameters and chemistry parameters by mean changes from baseline, individual subject changes form baseline (shifts to low or high) with respect to the normal range and abnormalities of potential clinical concern (PCC).

Hematology

There was no evidence of any clinically relevant mean changes from baseline or clinically relevant shifts from baseline in any of the hematology parameters across treatment groups. Table 29 provides a summary of subjects with hematology values outside the PCC range (Table 30). No significant differences were apparent across the placebo and GEn treatment groups.

Table 29: Subjects with Hematology Data Outside the PCC Range at any Post-Randomization Visit (Study PXN 110748)

Parameter	Number (%) of Subjects			
	PBO (N=95)	GEn 1200 mg/day (N=107)	GEn 2400 mg/day (N=82)	GEn 3600 mg/day (N=87)
Above PCC range (High)				
Eosinophils	6 (6)	2 (2)	3 (4)	4 (5)
Platelet count	1 (1)	1 (<1)	0	0
WBC Count	1 (1)	0	1 (1)	1 (1)
Below PCC range (Low)				
Hematocrit	1 (1)	4 (4)	0	1 (1)
Hemoglobin	1 (1)	2 (2)	0	0
Total Neutrophils	5 (5)	8 (7)	4 (5)	6 (7)
WBC Count	0	0	1 (1)	2 (2)

Data Source: CSR PXN110748, Table 3.27

GEn: gabapentin enacarbil; PBO: placebo; PCC: potential clinical concern; WBC: white blood cell

Source: Integrated Summary of Safety, p. 178

Table 30: Hematology Potential Clinical Concern (PCC) Ranges

Hematology Analyte	PCC Range	Standard Unit
Hemoglobin	Males ≤ 100 Females ≤ 90	g/L
Hematocrit	Males ≤ 0.32 Females ≤ 0.28	Proportion of 1.0
White Blood Cell Count	≤ 2.8 or ≥ 16	x 10^9/L
Neutrophils (Abs)	≤ 1.8	x 10^9/L
Eosinophils (Abs)	> 0.8	x 10^9/L
Platelets	≤ 100 or ≥ 550	x 10^9/L

Source: Summary Document Analysis Plan for Gabapentin Enacarbil PHN, Integrated Summary of Safety, p. 33

In the NDA review dated February 9, 2010 for the indication RLS, the medical officer, Dr. Susanne Goldstein, concluded that there does not appear to be a dose dependency for any of the hematologic abnormalities presented. She noted that there is no difference in drug treatment groups and placebo on any hematologic parameters with the exception of low RBC being greater in 1800 mg GEn cohort.

Reviewer's Note: It appears to this reviewer that the low RBC count identified in the 1800 mg cohort was not drug related, since there was no apparent effect of GEn on RBC count in the highest dose cohort (2400 mg).

Clinical Chemistry

In PHN Study PXN110748 there was no evidence of any clinically relevant mean changes from baseline or clinically relevant shifts from baseline in any of the chemistry parameters across treatment groups. Table 31 provides a summary of subjects with chemistry values outside the PCC range (Table 32). No significant differences were apparent across the placebo and GEn treatment groups. These findings are consistent with the medical officer review for RLS dated February 9, 2010, which did not identify a clear dose response for abnormal clinical chemistry values.

Table 31: Subjects with Clinical Chemistry Data Outside the PCC Range at any Post-Randomization Visit (Study PXN 110748)

Parameter	Number (%) of Subjects			
	PBO (N=95)	GEn 1200 mg/day (N=107)	GEn 2400 mg/day (N=82)	GEn 3600 mg/day (N=87)
Above PCC Range (High)				
ALT	0	0	0	1 (1)
AST	1 (1)	2 (2)	0	0
Carbon Dioxide/Bicarbonate	0	1 (<1)	0	0
Chloride	2 (2)	0	1 (1)	1 (1)
Cholesterol	16 (17)	12 (11)	10 (12)	13 (15)
Creatine Kinase	8 (9)	14 (13)	8 (10)	9 (11)
Creatinine	0	0	0	1 (1)
Phosphorous, inorganic	0	0	1 (1)	0
Potassium	0	0	2 (2)	2 (2)
Total Bilirubin	1 (1)	1 (<1)	0	1 (1)
Urea/BUN	1 (1)	0	2 (2)	2 (2)
Below PCC Range (Low)				
Calcium	0	0	0	1 (1)
Carbon Dioxide/Bicarbonate	5 (5)	8 (7)	3 (4)	6 (7)
Chloride	0	0	1 (1)	1 (1)
Phosphorous, inorganic	3 (3)	4 (4)	1 (1)	3 (4)
Potassium	0	0	0	1 (1)
Sodium	0	1 (<1)	0	1 (1)

Data Source: CSR PXN110748, Table 3.33
ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; ; GEn: gabapentin enacarbil
PBO: placebo; PCC: potential clinical concern
Source: Integrated Summary of Safety, p. 179

Table 32: Chemistry Potential Clinical Concern (PCC) Ranges

Chemistry Analyte	PCC Range	Standard Unit
Sodium	≤ 127 or ≥ 153	mmol/L
Potassium	≤ 3.0 or ≥ 6.0	mmol/L
Chloride	≤ 92 or ≥ 112	mmol/L
Bicarbonate	≤ 18 or ≥ 36	mmol/L
Blood Urea Nitrogen (BUN)	≥ 14.28	mmol/L
Creatinine	≥ 176.8	µmol/L
Protein (Total)	< 45 or > 100	g/L
Albumin	< 28 or > 65	g/L
Bilirubin (Total)	≥ 34.2	µmol/L
ALT	≥ 3 x ULN, ≥ 5 x ULN, ≥ 10 x ULN	U/L
AST	≥ 3 x ULN, ≥ 5 x ULN, ≥ 10 x ULN	U/L
Alkaline Phosphatase	≥ 3 x ULN	U/L
Glucose (random)	≤ 2.7755 or ≥ 11.102	mmol/L
Calcium	≤ 1.8962 or ≥ 2.86925	mmol/L
Phosphorus, Inorganic	13-59 years ≤ 0.71038 or ≥ 1.77595 60+ years ≤ 0.61351 or ≥ 1.80824	mmol/L
Cholesterol	≤ 1.6809 or ≥ 6.465	mmol/L
Creatine Phosphokinase (CPK)	Males ≥ 330 Females ≥ 245	U/L

Source: Summary Document Analysis Plan for Gabapentin Enacarbil PHN, Integrated Summary of Safety, p. 33

7.4.3 Vital Signs

There did not appear to be a significant effect of GEn on heart rate or blood pressure in the three Phase 2 PHN studies. Table 33 presents a summary of the subjects with blood pressure and heart rate outside the clinical concern range, collected at any post-randomization visit during Study PXN110748. There was no apparent clinically significant difference seen across the GEn or placebo groups. The findings in this review were consistent with the findings of the medical officer in the RLS NDA review, who did not identify a significant effect of the drug on blood pressure, respiratory rate or heart rate.

Table 33: Summary of Subjects with Blood Pressure and Heart Rate Outside Clinical Concern Range at Any Visit Post-Randomization (Study PXN110748)

Parameter	Number (%) of Subjects			
	PBO N = 95	GEn 1200 mg/day N = 107	GEn 2400 mg/day N = 82	GEn 3600 mg/day N = 87
SBP, n	95	107	82	86
> Clinical concern range	4 (4)	10 (9)	4 (5)	3 (3)
< Clinical concern range	0	0	0	0
Increase ≥20 mmHg from baseline	18 (19)	18 (17)	15 (18)	21 (24)
Increase ≥40 mmHg from baseline	2 (2)	2 (2)	1 (1)	1 (1)
Decrease ≤-20 mmHg from baseline	21 (22)	38 (36)	24 (29)	25 (29)
Decrease ≤-40 mmHg from baseline	5 (5)	6 (6)	0	0
DBP, n	95	107	82	86
> Clinical concern range	7 (7)	12 (11)	7 (9)	8 (9)
< Clinical concern range	0	0	0	0
Increase ≥10 mmHg from baseline	25 (26)	30 (28)	31 (38)	26 (30)
Increase ≥20 mmHg from baseline	6 (6)	4 (4)	6 (7)	7 (8)
Decrease ≤-10 mmHg from baseline	42 (44)	57 (53)	41 (50)	38 (44)
Decrease ≤-20 mmHg from baseline	7 (7)	12 (11)	7 (9)	9 (10)
HR, n	95	107	82	86
> Clinical concern range	1 (1)	1 (<1)	0	0
< Clinical concern range	1 (1)	2 (2)	2 (2)	1 (1)
Increase ≥15 bpm from baseline	38 (40)	29 (27)	20 (24)	32 (37)
Increase ≥30 bpm from baseline	4 (4)	5 (5)	0	1 (1)
Decrease ≤-15 bpm from baseline	8 (8)	12 (11)	11 (13)	5 (6)
Decrease ≤-30 bpm from baseline	0	0	0	0

Data Source: CSR PXN110748 Table 3.41
DBP: diastolic blood pressure; GEn: gabapentin enacarbil; HR: heart rate; PBO: placebo; SBP: systolic blood pressure
PCC Criteria: SBP (mmHg) <80 or >160; DBP (mmHg) <50 or >90; HR (bpm) <50 or >120
Source: Integrated Summary of Safety, p. 182

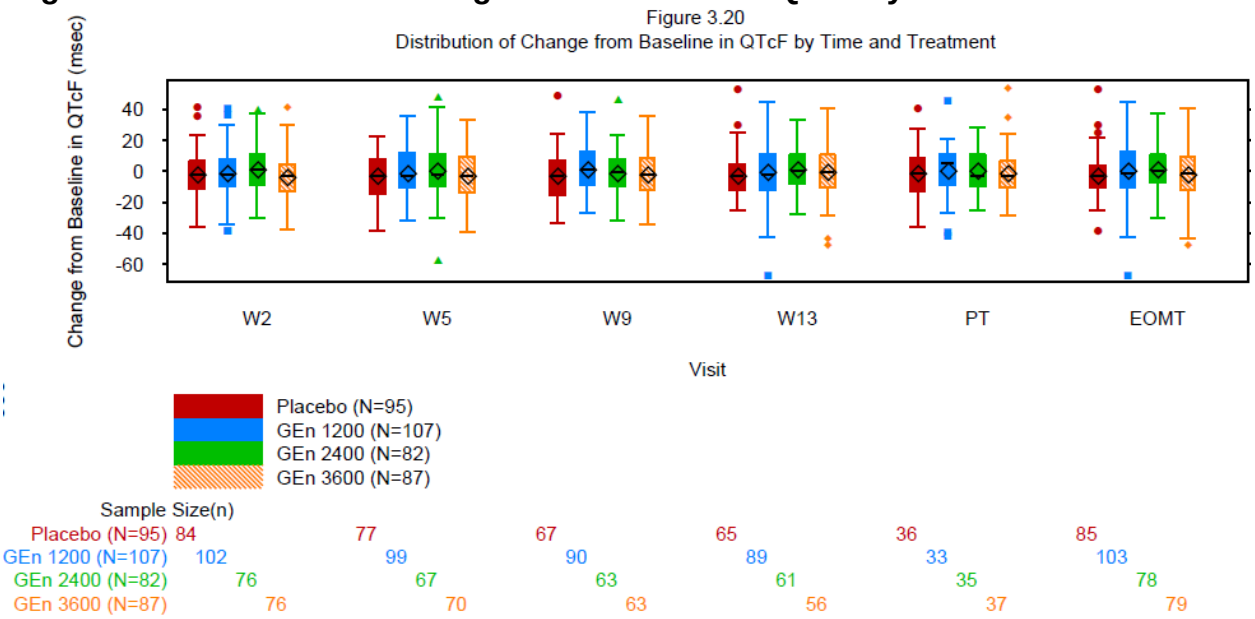
7.4.4 Electrocardiograms (ECGs)

12-Lead ECGs were performed in Study PXN110748 at Screening or Baseline and at all relevant treatment visits. The ECG findings did not demonstrate a clinically significant effect of GEn on QT interval. This conclusion is consistent with the findings in the previous NDA review for RLS where the medical officer concluded that there did not appear to be a drug effect on QT interval.

QT interval changes from baseline were calculated with Fridericia's correction (QTcF) and Bazett's correction (QTcB) for Study PXN110748. As shown in the Figure 4 below that displays the distribution in changes from baseline in QTcF there does not appear to be a clinically significant effect of GEn on QT interval. The maximum QTcF changes from baseline for any subject in the different treatment arms were 53, 45, 48 and 54

msec for placebo, GEn 1200, GEn 2400 and GEn 3600 treatment groups, respectively. The maximum QTcB changes from baseline were 68, 59, 56 and 61 msec for placebo, GEn 1200, GEn 2400 and GEn 3600 treatment groups, respectively. No subject had a QTcF change from baseline greater than 60 msec. However, there was one subject in the GEn 3600 mg group and one subject in the placebo group with a QTcB change from baseline greater than 60 msec. No subject in any treatment group had a QTcF greater than 480 msec. No subject in any treatment group had a QTcB greater than 500 msec.

Figure 4: Distribution of Change from Baseline in QTcF by Time and Treatment



Note: The 'EOMT' value reflects the week 13 assessment; for subjects without a week 13 visit, this value reflects the assessment collected at the withdrawal visit, as long as it occurred within one day of last dose of study medication; otherwise this is the last post-baseline assessment collected on or before date of last dose of study medication, and may include data collected during the up-titration period.
Note: The horizontal line within each box represents the median; the diamond symbol represents the mean.
Note: An ECG will only be performed at the Post Treatment visit if clinically indicated.
Source: Table 3.42
zd3045: /arenv/arprod/gsk1838262/pxn110748/final/drivers/f_safe_eg8_qtcf.sas 10SEP2009 20:19

Source: PXN110748 Study Report, p. 621

7.4.5 Special Safety Studies/Clinical Trials

Effects on Driving

In study XP083, a 2-week simulated driving study in patients with RLS, a daily single 1,200-mg dose of GEn caused significant impairment within 2 hours and for up to 14 hours after dosing. The patients taking 1200 mg of GE for 2-weeks had driving impairments that were very similar to patients tested at Tmax after receiving 50 mg of diphenhydramine. Patients with RLS may be at increased risk of impaired driving due to somnolence, but whether the impairment is related to somnolence or other effects of GEn is unknown.

The risk of driving impairment due to GEn in PHN can be addressed through appropriate labeling. Patients should be advised not to drive a car or operate other complex machinery until they have gained sufficient experience on GEn to assess whether GEn impairs their ability to perform these tasks.

7.4.6 Immunogenicity

This product does not raise concerns regarding immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There appeared to be a dose response for the following adverse reactions occurring at ≥2% at 1200 mg/day: dizziness, somnolence, fatigue and insomnia. The following adverse reactions reported as ≥2% at 2,400 mg/day and/or 3,600 mg/day but <2% at 1,200 mg/day appeared to be dose-related: balance disorder, confusional state, depression, dry mouth, flatulence, increased appetite, irritability, and vertigo.

7.5.2 Time Dependency for Adverse Events

In Study PXN110748 somnolence occurred early on but resolved within 4 to 5 weeks in about 70% of the subjects who developed somnolence. This is consistent with the medical officer review for the indication of RLS where it was noted that somnolence/sedation appeared to resolve within two weeks, particularly with GEn 600 mg.

7.5.3 Drug-Demographic Interactions

Geriatric Population
In study PXN110748, the 12-week, double-blind, placebo-controlled study of GEn for the management of PHN, 37% of patients were 65 to 74 years of age and 13% were 75 years of age and older. The overall incidence of adverse events was comparable among the patients aged ≥18 to <65 years, ≥65 to <74 years and ≥75 years (Table 34).

Table 34: Adverse Events Reported in At Least 5% of the GEn All Doses Group by Age Group in Study PXN110748

	Number (%) of Subjects by Age Group (years)														
	PBO (N=95)			GEn 1200 mg (N=107)			GEn 2400 mg (N=82)			GEn 3600 mg (N=87)			GEn All Doses (N=276)		
	≥18-<65 (N=50)	≥65-74 (N=29)	≥75 (N=16)	≥18-<65 (N=53)	≥65-74 (N=42)	≥75 (N=12)	≥18-<65 (N=39)	≥65-74 (N=35)	≥75 (N=8)	≥18-<65 (N=45)	≥65-74 (N=26)	≥75 (N=16)	≥18-<65 (N=137)	≥65-74 (N=103)	≥75 (N=36)
Any Event	35 (70)	17 (59)	11 (69)	37 (70)	28 (67)	10 (83)	32 (82)	29 (83)	3 (38)	37 (82)	21 (81)	13 (81)	106 (77)	78 (76)	26 (72)
Preferred Term															
Dizziness	7 (14)	5 (17)	2 (13)	8 (15)	8 (19)	2 (17)	7 (18)	12 (34)	2 (25)	12 (27)	10 (38)	4 (25)	27 (20)	30 (29)	8 (22)
Headache	4 (8)	4 (14)	1 (6)	5 (9)	6 (14)	0	6 (15)	2 (6)	0	6 (13)	0	0	17 (12)	8 (8)	0
Somnolence	5 (10)	3 (10)	0	6 (11)	2 (5)	3 (25)	3 (8)	6 (17)	0	7 (16)	4 (15)	1 (6)	16 (12)	12 (12)	4 (11)
Nausea	3 (6)	1 (3)	1 (6)	5 (9)	3 (7)	1 (8)	1 (3)	2 (6)	0	7 (16)	0	1 (6)	13 (9)	5 (5)	2 (6)
Fatigue	0	0	1 (6)	2 (4)	1 (2)	2 (17)	4 (10)	0	0	5 (11)	2 (8)	2 (13)	11 (8)	3 (3)	4 (11)
Edema peripheral	0	0	0	4 (8)	1 (2)	1 (8)	4 (10)	1 (3)	1 (13)	2 (4)	1 (4)	2 (13)	10 (7)	3 (3)	4 (11)
Diarrhea	5 (10)	0	0	4 (8)	2 (5)	0	1 (3)	1 (3)	0	3 (7)	2 (8)	1 (6)	8 (6)	5 (5)	1 (3)
Arthralgia	2 (4)	0	1 (6)	3 (6)	3 (7)	0	2 (5)	1 (3)	1 (13)	2 (4)	1 (4)	0	7 (5)	5 (5)	1 (3)
Dry mouth	2 (4)	0	0	1 (2)	0	0	2 (5)	1 (3)	0	4 (9)	0	0	7 (5)	1 (<1)	1 (3)
Insomnia	2 (4)	0	0	1 (2)	2 (5)	0	3 (8)	1 (3)	0	3 (7)	1 (4)	2 (13)	7 (5)	4 (4)	2 (6)
Blood CPK increased	1 (2)	0	0	3 (6)	0	0	3 (8)	0	0	1 (2)	0	0	7 (5)	0	0
Constipation	3 (6)	0	2 (13)	3 (6)	2 (5)	2 (17)	1 (3)	3 (9)	0	2 (4)	1 (4)	1 (6)	6 (4)	6 (6)	3 (8)
Nasopharyngitis	3 (6)	0	2 (13)	2 (4)	1 (2)	2 (17)	2 (5)	1 (3)	0	2 (4)	2 (8)	1 (6)	6 (4)	4 (4)	3 (8)
Back pain	2 (4)	1 (3)	0	2 (4)	0	2 (17)	2 (5)	2 (6)	0	0	1 (4)	1 (6)	4 (3)	3 (3)	3 (8)
Balance disorder	0	0	0	0	0	0	0	2 (6)	1 (13)	1 (2)	0	2 (13)	1 (<1)	2 (2)	3 (8)
Weight increased	1 (2)	0	0	1 (2)	0	2 (17)	2 (5)	2 (6)	0	2 (4)	1 (4)	1 (6)	5 (4)	3 (3)	3 (8)
Hypoesthesia	3 (6)	0	0	1 (2)	0	2 (17)	1 (3)	0	0	1 (2)	0	0	3 (2)	0	2 (6)
Influenza	0	0	0	1 (2)	1 (2)	0	1 (3)	0	0	0	0	2 (13)	2 (1)	1 (<1)	2 (6)

Source: Module 5.3.5.3 Integrated Summary of Safety, pg. 199

7.5.4 Drug-Disease Interactions

Since GEn, is nearly completely eliminated by the kidneys, subjects with renal insufficiency need to be dosed accordingly. The pharmacokinetics of GEn was examined in subjects with renal impairment. There is an approximately linear relationship between gabapentin clearance and creatinine clearance (CrCL). For every 2 fold increase in CrCL, there is an approximately 1.6 fold decrease in gabapentin CL/F.

7.5.5 Drug-Drug Interactions

The reader is referred to Section 4.2 for information on drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Pancreatic Acinar Cell Carcinoma

At the request of the Division of Neurology Products, the sponsor performed two case-control studies based on data from the General Practice Research Database (GPRD) in the UK, which were designed to evaluate whether or not gabapentin use is associated

with pancreatic cancer. The GPRD database contains computerized medical records for about 3.2 million patients.

The two studies (4774 and 4931) submitted in the RLS NDA, were nearly identical in design, except that Study 4774 did not exclude patients with a history of cancer (Study 4931 did exclude such patients), and Study 4774 evaluated only pancreatic and renal tumors; Study 4931 evaluated numerous tumor types. The study periods began on 1/1/93, and ended on 12/31/08.

The Division of Neurology Products concluded that although the epidemiologic study the sponsor performed in the GPRD dataset yielded odds ratios of about 2 for pancreatic (and renal) cancer, results that were nominally statistically significant, these results do not, in any way, establish that gabapentin causes pancreatic cancer in people, for numerous reasons. In particular, the finding arises entirely from the first tertiles of all measures of exposure. The maximum duration of use of gabapentin in the first tertile was 1.55 months; the maximum cumulative dose of gabapentin in the first tertile was 33.6 gms; the maximum number of prescriptions in the first tertile was 2. The mean duration of exposure in patients treated with gabapentin who had pancreatic cancer was about 6 months. No significant findings were noted in the second and third tertiles of any measure of exposure. Gabapentin cannot credibly be considered to be causally related to these tumors, given the short-term exposures seen in patients with tumors.

7.6.2 Human Reproduction and Pregnancy Data

No formal clinical trials have been conducted in pregnant women. During the clinical development program of GEn for the treatment of PHN, there was one pregnancy in the phase 2 PHN studies (Subject PXN110748/5756). The outcome was a healthy normal neonate.

> Subject 005756, a 39 year old woman, was enrolled in this study for the treatment of neuropathic pain associated with postherpetic neuralgia. The subject was randomized to GEn 3600 mg and received drug twice per day from March 11, 2009 until April 19, 2009. The subject gave birth by cesarean section at 39 weeks gestation age on (b) (6) to a normal female infant. The baby weighed 2902.99 grams and was 43.3 cm in length.

There were 3 additional pregnancies in the development program for GEn for other indications. The outcome of the pregnancies in two subjects was a healthy neonate and the outcome in the remaining pregnancy was unknown.

It is unknown whether GEn or gabapentin derived from GEn is excreted in human breast milk; however, it has been shown that gabapentin is present in human breast milk following oral administration of gabapentin.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies have been performed to date with GEn. The Applicant will not be required to conduct pediatric studies to fulfill the requirements of the Pediatric Research Equity Act since GEn was granted orphan drug status for "management of postherpetic neuralgia in adults" and furthermore the incidence of PHN is too low in the pediatric population to make pediatric studies feasible.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
The Applicant identified no cases of overdose using an extensive list of adverse event preferred terms and verbatim terms to search the PHN studies, pain studies in other indications, RLS studies and clinical pharmacology studies. Using this broad search strategy, several potential cases for further evaluation were identified. However, further review by the Applicant revealed these cases to be false positives (i.e., food poisoning and depression in Study PXN110748). As additional support of the safety of GEn the Applicant noted that single doses up to 6000 mg were administered without titration in the Phase 1 clinical pharmacology studies and the nature of adverse events was similar to that reported in the Phase 2 and 3 clinical studies.

Drug Abuse Potential
The Applicant identified no reports of abuse potential and concluded that across the three PHN studies, results from the search of AEs potentially indicative of abuse liability, using search terms provided by the Controlled Substance Staff (CSS), do not raise issues of concern. The Applicant also noted that apart from known and expected AEs (e.g., dizziness and somnolence), the occurrence of AEs considered possibly associated with abuse potential was infrequent.

Reviewer's Note: Although, the Applicant is correct in maintaining that the most frequent AEs of dizziness and somnolence are known and expected AEs, there were also infrequent AEs of 'feeling drunk', 'euphoric mood' and 'visual hallucination' that occurred only in GEn treatment groups in Study PXN110748. However, the incidence of these AEs was too low to make any definitive conclusions regarding their significance. Gabapentin is not known to be active at receptor sites associated with drugs of abuse and animal studies have not been confirmatory. However, very low rates of postmarketed cases of gabapentin misuse and abuse were reported and gabapentin was frequently identified in polypharmacy abuse and addiction cases. As with any CNS active drug, patients should be evaluated for a history of drug abuse and observed for signs and symptoms of misuse or abuse. Postmarketing adverse events that may be related to drug abuse should be monitored.

Withdrawal

There was one case of withdrawal seizure previously reported in the NDA submission for RLS. The subject in XP13512 was found to have a seizure focus on EEG.

In Study PXN110748 there was no clear evidence of withdrawal symptoms associated with GEn use. However, slightly more patients had symptoms potentially related to withdrawal in the GEn treatment group than placebo group (Table 35). Dr. Stephen Sun concluded in his Controlled Substance Staff consult dated March 21, 2012 that in general, the rate of gabapentin misuse and abuse appears to be relatively low when considering the large denominator of prescriptions. He noted that published articles include a few case reports of gabapentin withdrawal symptoms (symptoms reversible after gabapentin was re-initiated) and abuse behaviors (high-dose intoxication with and without concomitant use of other illicit and legitimate drugs). Dr. Sun concluded the following:

1. Continue surveillance of the misuse and abuse of these products (gabapentin, pregabalin, and GEn) for two to five more years consistent with OSE's recommendation
2. Label should reflect what is currently known on the abuse and dependence potential of GEn. Such language should include the summary of postmarketed human experience with gabapentin. For example, the label should include the following:

9.1 Controlled Substance
GEn is not a scheduled drug.

9.2 Abuse
(b) (4)

9.3 Dependence
(b) (4)

At this time no additional action is required except to continue surveillance for possible postmarketing cases of withdrawal adverse reactions.

Table 35: Adverse Events during Down-Titration in at least 1% of Subjects in any GEn Group (Study PXN110748)

	Number (%) of Subjects				
	PBO (N=95)	GEn 1200 mg/day (N=107)	GEn 2400 mg/day (N=82)	GEn 3600 mg/day (N=87)	GEn All Doses (N=276)
Any Event with Onset during Down-Titration	2 (2)	13 (12)	10 (12)	14 (16)	37 (13)
Preferred Term					
Insomnia	0	1 (<1)	1 (1)	4 (5)	6 (2)
Nausea	0	0	1 (1)	3 (3)	4 (1)
Depression	0	1 (<1)	0	2 (2)	3 (1)
Joint sprain	0	2 (2)	0	0	2 (<1)
Postherpetic neuralgia	0	2 (2)	0	0	2 (<1)

Data Source: PHN ISS, Table 5.18
GEn: gabapentin enacarbil; PBO: placebo
Note: Events are ordered by decreasing frequency in the GEn All Doses group.

Source: Integrated Summary of Safety, p. 213

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

The Periodic Safety Update Reports were reviewed and do not affect the overall benefit risk analysis of the drug.

9 Appendices

9.1 Literature Review/References

Refer to Section 5.3.4 for a summary of two published articles provided by the Applicant on the use of gabapentin in the treatment of PHN.

9.2 Labeling Recommendations

Recommended changes in the label regarding abuse and dependence are discussed in Section 7.6.4.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held for this product.

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/s/

ROBERT A LEVIN
05/05/2012

FRANK PUCINO
05/05/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-399/S-003

CHEMISTRY REVIEW(S)

22-399try Review #1	**1. Division ONDQA**	**2. NDA & Suppl. Number** 22-399/SCE-003
3. Name and Address of Applicant GlaxoSmithKline Attn: Eric B. Benson, Senior Director, Regulatory Affairs. Five Moore Drive, P.O. Box 13398 Research Triangle Park, NC 27709		**4. DATE** **Submission** **PDUFA** 8/9/11 2/9/12
5. Name of Drug: HORIZANT	**6. Nonproprietary:** gabapentin enacarbil Extended Release.	
7. Supplement, PR, Provides for: A new indication.		**8. Amendment Date**
9. Pharmacological Category	**10. How Dispensed** Rx	**11. Related Documents**
12. Dosage Form: Extended Release Tablets.	**13. Potency(ies):** 600 mg and 300 mg (see review for details)	
14. Chemical Name and Structure see USAN		

15. Comments:

Currently approved indication:

For the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS)

The currently proposed new indication:

HORIZANT (gabapentin enacarbil) Extended-Release Tablets are indicated for the management of postherpetic neuralgia in adults.

300 mg Strength:

A supplement, S-002, for the 300 mg tablet was submitted dated 6/24/11. The supplement was approved on 12/23/2011.

There are no CMC changes in this supplemental application.

16. Conclusions and Recommendations:

Submission of the CMC is complete. Approval based on the CMC submission only.

17. Name: Review Chemist	**Signature**	**Date**
Bart Ho, Chemist		
Branch Chief James D. Vidra, Ph.D.	Signature	Date

Doc ID: 22399SCE003 new indication GSK.doc

REVIEW NOTES

Changes related to CMC:

Request for the approval of a new strength, 300 mg was first submitted dated 6/24/11. It was approved 12/23/2011.

There are no other CMC changes in this supplemental application.

Labeling related to CMC:

"DESCRIPTION"

HORIZANT (gabapentin enacarbil) is a prodrug of gabapentin. Gabapentin enacarbil is described as (1-{[({(1*RS*)-1-[(2-Methylpropanoyl)oxy]ethoxy}carbonyl)amino]methyl} cyclohexyl) acetic acid. It has a molecular formula of $C_{16}H_{27}NO_6$ and a molecular weight of 329.39. It is a racemate.

Gabapentin enacarbil is a white to off-white crystalline solid with a melting onset of approximately 64°C and a solubility of 0.5 mg/mL in water and 10.2 mg/mL in phosphate buffer (pH 6.3).

HORIZANT is administered orally. Each HORIZANT Extended-Release Tablet contains 300 mg or 600 mg of gabapentin enacarbil and the following inactive ingredients: colloidal silicon dioxide, dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium stearate, sodium lauryl sulfate, and talc. The 300 mg tablets also contain red ferric oxide. **[Text consistent with Prior Approval submitted on 24JUN2011]**

Evaluation: *Adequate*

There are no changes in the drug product information. Formulation remains the same.

HOW SUPPLIED/STORAGE AND HANDLING:

HORIZANT Extended-Release Tablets containing 300 mg of gabapentin enacarbil are red, with occasional black/grey spots, oval-shaped tablets debossed with "GS TF7" and 600 mg of gabapentin enacarbil are white to off-white, with occasional black/(b) (4) grey spots, oval-shaped tablets debossed with "GS LFG". They are supplied as follows:

300 mg: NDC 0173-0832-13: Bottles of 30 **[Text consistent with Prior Approval submitted on 24JUN2011]**

600 mg: NDC 0173-0806-01: Bottles of 30 Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Do not remove desiccants. Dispense in original bottle.

Evaluation: Adequate

Environmental Assessment:

Claim of Categorical Exclusion:

The proposed action is subject to the categorical exclusion listed in 21 CFR Part 25.31(b). GlaxoSmithKline has reviewed market forecasts, indications, and dosage information, and estimates that this action will not cause the concentration of the drug substance active moiety Gabapentin to be (b) (4) or greater at the point of entry into the aquatic environment.

GlaxoSmithKline does not have knowledge of any extraordinary circumstances that might cause this action to have a significant affect on the quality of the human environment.

Evaluation: Acceptable.

To propose categorical exclusion per 21 CFR Part 25.31 (b) is acceptable. Preparation of an EA report is not needed.

Conclusions and Recommendations:

Recommend approval pending on the medical officer's review of the current supplement.

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/s/

BARTHOLOME C HO
06/01/2012

JAMES D VIDRA
06/01/2012

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22-399try Review #1	**1. Division ONDQA**	**2. NDA & Suppl. Number** 22-399/SCE-003
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16. Conclusions and Recommendations:

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17. Name: Review Chemist	**Signature**	**Date**
Bart Ho, Chemist		
Branch Chief James D. Vidra, Ph.D.	Signature	Date

Doc ID: 22399SCE003 new indication GSK.doc

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Labeling related to CMC:

"DESCRIPTION"

HORIZANT (gabapentin enacarbil) is a prodrug of gabapentin. Gabapentin enacarbil is described as (1-{[({(1*RS*)-1-[(2-Methylpropanoyl)oxy]ethoxy}carbonyl)amino]methyl} cyclohexyl) acetic acid. It has a molecular formula of $C_{16}H_{27}NO_6$ and a molecular weight of 329.39. It is a racemate.

Gabapentin enacarbil is a white to off-white crystalline solid with a melting onset of approximately 64°C and a solubility of 0.5 mg/mL in water and 10.2 mg/mL in phosphate buffer (pH 6.3).

HORIZANT is administered orally. Each HORIZANT Extended-Release Tablet contains 300 mg or 600 mg of gabapentin enacarbil and the following inactive ingredients: colloidal silicon dioxide, dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium stearate, sodium lauryl sulfate, and talc. The 300 mg tablets also contain red ferric oxide. **[Text consistent with Prior Approval submitted on 24JUN2011]**

Evaluation: *Adequate*

There are no changes in the drug product information. Formulation remains the same.

HOW SUPPLIED/STORAGE AND HANDLING:

HORIZANT Extended-Release Tablets containing 300 mg of gabapentin enacarbil are red, with occasional black/grey spots, oval-shaped tablets debossed with "GS TF7" and 600 mg of gabapentin enacarbil are white to off-white, with occasional black/(b) (4) grey spots, oval-shaped tablets debossed with "GS LFG". They are supplied as follows:

300 mg: NDC 0173-0832-13: Bottles of 30 **[Text consistent with Prior Approval submitted on 24JUN2011]**

600 mg: NDC 0173-0806-01: Bottles of 30 Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Do not remove desiccants. Dispense in original bottle.

Evaluation: Adequate

Conclusions and Recommendations:

Recommend approval pending on the medical officer's review of the current supplement.

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/s/

BARTHOLOME C HO
01/27/2012

JAMES D VIDRA
01/27/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-399/S-003

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA AND ADDICTION PRODUCTS

PHARMACOLOGY/TOXICOLOGY MEMORANDUM

NDA Application number:	**22-399**
Supplement number:	**003**
eCTD Sequence number:	**0056**
CDER stamp date:	**August 9, 2011**
Product:	**Horizant ™, Gabapentin enacarbil, extended-release tablets**
Indication:	**management of postherpetic neuralgia (PHN) in adults**
Sponsor:	**GlaxoSmithKline (GSK)**
Review Division:	**Division of Anesthesia, Analgesia and Addiction Products**
Reviewer:	**Armaghan Emami, Ph.D.**
Supervisor/Team Leader:	**Adam Wasserman, Ph.D.**
Division Director:	**Bob Rappaport, M.D.**
Project Manager:	**Sharon Turner Rinehardt**

1 EXECUTIVE SUMMARY

1.1 INTRODUCTION

The present NDA supplement (sNDA) pertains to Horizant® (Gabapentin enacarbil, GEn) which is submitted as a 505(b)(2) application with reference made to NDA 20-235 to rely on previous findings of safety and efficacy for the approved listed drug Neurontin® (gabapentin) and for support of current product labeling of Horizant.

GEn, a prodrug of gabapentin, is rapidly converted to gabapentin upon absorption from the intestinal lumen. The systemic exposure to intact prodrug is very low; less than 0.5% of the corresponding systemic exposure to gabapentin.

Horizant was approved by the FDA for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults on 06 April 2011. The recommended dose of Horizant for treatment of RLS is 600 mg/day. However, the proposed dosing regimen for the management of PHN is 1200 mg/day (600 mg twice daily).

The existing nonclinical development program submitted to the RLS NDA was reviewed by the Division of Neurologic Products over two NDA cycles and a nonclinical safety assessment supported oral administration of GEn at a daily dose of up to 1200 mg. (b) (4) The same drug substance and drug product approved for the treatment of RLS is proposed for use in the management of PHN. Therefore, no additional nonclinical studies are considered necessary to support the current application.

1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS

The original NDA review for treatment of RLS contains a nonclinical safety assessment of oral administration of GEn at daily dose up to 1200 mg. For more detail see the Pharmacology/Toxicology review by Dr. Terry Peters.

The table below is provided by the Applicant and this reviewer believes that the nonclinical data supports the MRHD of 1200 mg/day for treatment of PHN.

Table 3.1 Gabapentin Exposure Following Oral Administration of Gabapentin Enacarbil: Comparative Systemic Exposure in Mice, Rats, Rabbits, Monkeys and Humans

Species (Study Type) [Report No.]	GEn Dose (mg/kg/day)	Gabapentin Toxicokinetic Data	
		AUC_{0-24}[a] (µg.h/mL)	Multiple of Clinical Exposure[b]
Repeat Dose Studies			
Mouse (13 week) [RD2008/00324/00]	500	109	1.09
	2000	591	5.91
	5000 (NOAEL)	**1620**	**16.2**
Rat (13 week) [RD2007/01523/00]	500	462	5.45
	2000 (NOAEL)	**1590**	**18.8**
	5000	5290	62.4
Rat (26 week) [RD2007/01526/00]	500	362	4.27
	2000 (NOAEL)	**1470**	**17.3**
	5000	3130	36.9
Monkey (13 week) [RD2007/01524/00]	500	775	7.75
	1000	1550	15.5
	2000 (NOAEL)	**2670**	**26.7**
Monkey (39 week) [RD2007/01528/00]	250	316	3.16
	1000	1600	16.0
	2000 (NOAEL)	**2860**	**28.6**
Reproductive and Developmental Studies			
Rat (EFD)[c] [RD2008/00144/00]	200	195	2.30
	1000 (NOAEL)	**988**	**11.7**
	5000	3310	39.1
Rabbit (EFD) [RD2008/00146/00]	200	311	3.11
	500	944	9.44
	2500 (NOAEL)	**3040**	**30.4**
Clinical Studies			
Human	24[d] (1200 mg)	100[e]	1

Key: EFD = Embryofetal development. GEn = Gabapentin enacarbil.
NOAEL = No observed adverse effect level.

a = Steady state values (blood) from toxicity studies (Day Last or at 26 weeks in the 39 week study in monkeys), mean of combined sexes.

b = Ratio of animal to human exposure calculated as ratio of mean C_{max} or AUC to mean human C_{max} or AUC (based on correction for blood/plasma concentration differences; 1.18 for rat and 1.0 for all other species).

c = As no toxicokinetic evaluations were conducted in the peri-/post-natal study [Report RD2008/00148/00], exposure data from the EFD study, which utilized the same doses, were used. The NOAEL for the peri-/post-natal study is 200 mg/kg/day.

d = Assumed 50 kg body weight.

e = The median steady state AUC_{0-24} of gabapentin after dosing GEn 1200 mg/day in patients with PHN [see m2.7.2, Summary of Clinical Pharmacology Studies, Section 3.1.4].

There was a concern about the pancreatic tumors observed in the rat in the previous review of this NDA which initially led to a Complete Response for the NDA due to an inadequate safety margin. However, the Applicant referred to the Agency's prior finding of safety for gabapentin (Neurontin). Carcinogenicity studies with gabapentin showed the same tumor finding in rats, although only in males. The Agency considered 1000 mg/kg to be the no-effect dose for the occurrence of carcinoma with direct gabapentin administration. Therefore, the Applicant provided new data for the NDA resubmission assessing the plasma exposure to gabapentin under conditions similar to those used in

the original gabapentin rat carcinogenicity study in order to bridge to the gabapentin exposures observed in the GEn study. For the RLS indication (MRHD: 600 mg/day), the exposure to gabapentin in the rat with 1000 mg gabapentin/kg was approximately 25 times higher than the human exposure and was intermediate between the exposures observed at 500 and 2000 mg/kg GEn. The 25-fold margin was considered acceptable as a margin for the RLS indication and allowed for approval.

For the present PHN indication (MRHD: 1200 mg/day), the exposure to gabapentin in the rat at 1000 mg gabapentin/kg was approximately 13 times higher than the intended human exposure for this indication. Therefore, the NOAEL for the pancreatic tumors in rats actually occurs at an exposure to gabapentin that is 13-fold higher than the clinical exposure. Table below is provided by the Applicant

Table 3.3 Exposure Margins for Gabapentin-Related Pancreatic Acinar Cell Tumors in Rats (Data ordered by AUC)

Gabapentin Enacarbil					Gabapentin		
Gabapentin Enacarbil Dose (mg/kg/day)	Gabapentin AUC (µg.h/mL)		Exposure Margins[a]		Gabapentin Dose (mg/kg/day)	Gabapentin AUC (µg.h/mL)	Exposure Margins[a]
	Male	Female	Male	Female			Male
5000	***6640***	***5870***	***66X***	***59X***			
2000	*1950*	1830	*20X*	18X	2000	***1780[b]***	18X
					1000	1300[b]	13X
500	572	544	6X	5X	250	515[c]	5X
0	0	0	-	-	0	0	-
1200 mg clinical	100		1X		1800 mg clinical	165[d]	~1.7X

Key: ***Bold italics*** denotes clearly carcinogenic. *Italics* denotes threshold/slight effect.
Data rows are ordered by AUC of ~500 µg.h/mL increments, grey background indicates no data.
Toxicokinetic data and clinical data are from steady-state plasma levels (or blood data converted to plasma).
a = Calculated based on the median estimate of gabapentin AUC (100 µg.h/mL) at a clinical dose of 1200 mg GEn [see m2.7.2, Summary of Clinical Pharmacology Studies, Section 3.1.4].
b = Males only [Report 2010N105806_00].
c = Radulovic, 1995b (combined gender data).
d = Median gabapentin AUC at a clinical dose of 1800 mg/day Neurontin [see m2.7.2, Summary of Clinical Pharmacology Studies, Table 3].

The potential carcinogenic risk of the proposed drug product is likely reduced given that PHN is not a chronic disorder that generally requires long-treatment (i.e., > 6 months). Therefore, the 13-fold margin is considered acceptable as a margin for the PHN indication

1.3 RECOMMENDATIONS

1.3.1 Approvability: From the non-clinical pharmacology toxicology perspective, this NDA may be approved.

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: Note the Applicant uses language from the approved Horizant prescribing information with adjusted dose margins based on the area-under-the-curve (AUC) plasma exposure with use of the higher total daily dose with Horizant for treatment of PHN. The final label may differ based on negotiations with Applicant and further internal discussion with the Division of Neurology Products.

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
(b) (4)		
	The no-effect dose for embryo-fetal developmental toxicity in rats (200 mg/kg/day) represents approximately 2 times the gabapentin exposure associated with the maximum	To be consistent with the following paragraph and to clarify that the margins are based on the gabapentin exposure with the MHRD.

(b) (4)	recommended human dose (MRHD) of 1,200 mg/day gabapentin enacarbil on an area under the curve (AUC) basis. The no-effect dose for embryo-fetal developmental toxicity in rabbits (500 mg/kg/day) represents approximately 9 times the gabapentin exposure associated with the MRHD of 1,200 mg/day gabapentin enacarbil on an AUC basis.	

(b) (4)		
	No changes recommended	
	No changes recommended	

(b) (4)		
(b) (4)	The precise mechanism by which gabapentin is efficacious in RLS and PHN is unknown. ~~The mechanism of action by which gabapentin is efficacious in PHN is unknown but in animal models of analgesia, gabapentin prevents allodynia (pain related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test), but does not alter immediate pain-related behaviors (rat tail~~	There is no need for presenting the animal models such as peripheral inflammation and neuropathic pain since these models are not necessarily predictive of human efficacy.

(b) (4)	~~flick test, formalin footpad acute phase). The relevance of these models to human pain is not known.~~	
		The applicant used exposure levels from a 13 week study in mice to bridge to 2 years carcinogenicity study. See table 3.1 and Appendix 1.

(b) (4)		
	The plasma exposures (AUC) for gabapentin at these doses are approximately (b) (4) 4, (b) (4) 17 and (b) (4) 37 times, resp ectively, that in humans at the MRHD.	According Dr. Lois Freed's review (submitted 4/05/2011) the Applicant chose the 3-month rat study because the 3 month study had more frequent sampling time. The sponsor noted that this was particularly important for estimates of exposure at the LD since the Tmax at that dose was 0.5 hours. However, we recommend using the 6- month rat study since the mean exposure level in the high dose group in 3-month study is unexpectedly much higher than other TK studies (see Appendix 2).
	At 1,000 mg/kg/day, the plasma AUC for gabapentin is estimated to be approximately (b) (4) 13 times that in humans at the MRHD.	Based on data providing from bridging study (Appendix 3) and Sponsor's table 3.3, the safety margin is 13X.

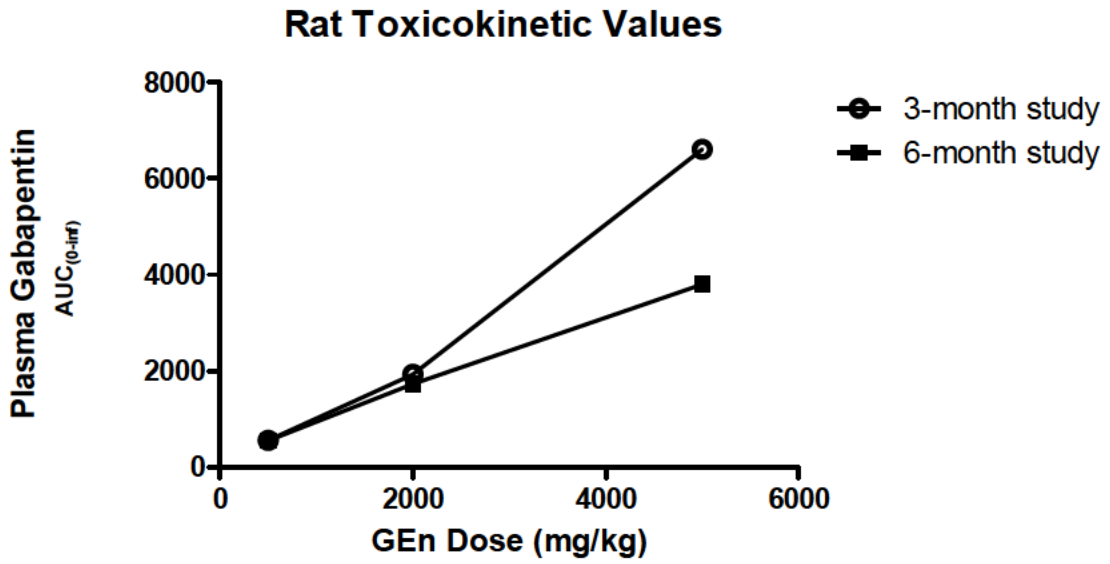
(b) (4)	The highest dose tested is approximately (b) (4) 39 times the MRHD on an AUC basis.	The applicant used exposure data from embryofetal development study since there was no TK evaluation in the peri-/post-natal study. Therefore, based on the data provided in Sponsor's table 3.1 the safety margin is 39X.

Appendix 1:

Table A1.3 (Continued) Listing of Toxicology Studies Performed with Gabapentin Enacarbil

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg/day)[a] or Concentration	Duration of Dosing	GLP	Testing Facility (b) (4)	Report No. (Study No.)	Location in NDA 022399
Carcinogenicity (continued)										
Pre-oncogenicity	Mouse (B6C3F1)	15M/15F (38M/38F[TK])	Oral (gavage)	GEn	500, 2000, 5000	13 weeks	Yes		RD2008/00324/00 (XP024)	Sequence 0004, m4.2.3.4.2
Carcinogenicity	Mouse (B6C3F1)	60M/60F	Oral (gavage)	GEn	500, 2000, 5000	2 years	Yes		RD2008/00346/00 (XP050)	Sequence 0004, m4.2.3.4.1
Carcinogenicity	Rat (Wistar)	60M/60F	Oral (gavage)	GEn	500, 2000, 5000	2 years	Yes		RD2008/00347/00 (XP051)	Sequence 0004, m4.2.3.4.1
Reproductive and Developmental Toxicity										
Fertility	Rat (SD)	25M	Oral (gavage)	GEn	200, 1000, 5000	4 weeks prior to cohabitation through cohabitation	Yes		RD2008/00147/00 (XP035)	Sequence 0004, m4.2.3.5.1
		25F				2 weeks prior to cohabitation through Day 7 pc				
EFD (dose range finding)	Rat (SD)	8F	Oral (gavage)	GEn	200, 500, 1500, 5000	Days 7 to 17 pc	Yes		RD2007/01534/00 (XP031)	Sequence 0004, m4.2.3.5.2
EFD	Rat (SD)	25F (6F[TK])	Oral (gavage)	GEn	200, 1000, 5000	Days 7 to 17 pc	Yes		RD2008/00144/00 (XP032)	Sequence 0004, m4.2.3.5.2
EFD (dose range finding)	Rabbit (NZW)	5F (3F[TK])	Oral (stomach tube)	GEn	200, 500, 1500, 5000	Days 7 to 19 pc	Yes		RD2008/00145/00 (XP033)	Sequence 0004, m4.2.3.5.2
EFD	Rabbit (NZW)	20F (3F[TK])	Oral (stomach tube)	GEn	200, 500, 2500	Days 7 to 19 pc	Yes		RD2008/00146/00 (XP034)	Sequence 0004, m4.2.3.5.2
Peri- & post-natal development	Rat (SD)	25F	Oral (gavage)	GEn	200, 1000, 5000	Day 7 pc to Day 20 pp	Yes		RD2008/00148/00 (XP036)	Sequence 0004, m4.2.3.5.3

Appendix 2:


Rat Toxicokinetic Values
Plasma Gabapentin AUC(0-inf)
8000
6000
4000
2000
0
0
2000
4000
6000
GEn Dose (mg/kg)
3-month study
6-month study

Appendix 3:

Rat bridging study (2010N105806_00):

2.0 SUMMARY TABLE

Table 2.1: Mean Toxicokinetic Parameters of Gabapentin in Blood and Plasma on Day 14 Following Repeated Oral Administration of Gabapentin in Diet for 14 Days in Male Wistar Rats

Matrix	Gabapentin Dose (mg/kg/day)	TK Parameters of Gabapentin		
		C_{max} (µg/mL)	T_{max} (hr)	AUC_{0-24} (µg*hr/mL)
Blood	1000	59.8	9.00	1090
	2000	79.7	9.00	1500
Plasma[a]	1000	71.1	9.00	1300
	2000	94.6	9.00	1780

[a] Gabapentin plasma concentrations were estimated from blood data using the following plasma to blood equation: gabapentin plasma concentrations (µg/mL) = 0.55 + 1.18 × gabapentin blood concentrations (µg/mL) (XenoPort Study Report XP100-TK).

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/s/

ARMAGHAN EMAMI
05/04/2012

ADAM M WASSERMAN
05/04/2012
I concur this efficacy supplement may be approved with agreement on labeling.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-399/S-003

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION-ADDENDUM

CLINICAL STUDIES

NDA/Serial Number:	22399 / 003
Drug Name:	Horizant (gabapentin enacarbil)
Indication(s):	Management of postherpetic neuralgia (PHN)
Applicant:	GlaxoSmithKline
Date(s):	Letter date: 8/9/11 PDUFA date: 6/9/11
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	Dionne Price, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAARP)
Clinical Team:	Medical Officer: Robert Levin, M.D. Medical Team Leader: Frank Pucino, Pharm.D.
Project Manager:	Sharon Turner-Rinehart

Keywords: NDA Review; Single study

Addendum to clarify the imputation of missing data for the continuous responder analysis

In my original review (5/10/12) I described the data set which was used in the continuous responder analysis as follows:

> I performed a continuous responder analysis, in which all patients who discontinue were classified as non-responders. For patients who completed the maintenance treatment period, the BOCF imputation was applied.

The results of that analysis were presented in Table 5 and Figure 2 of my review. The information was also represented in the label.

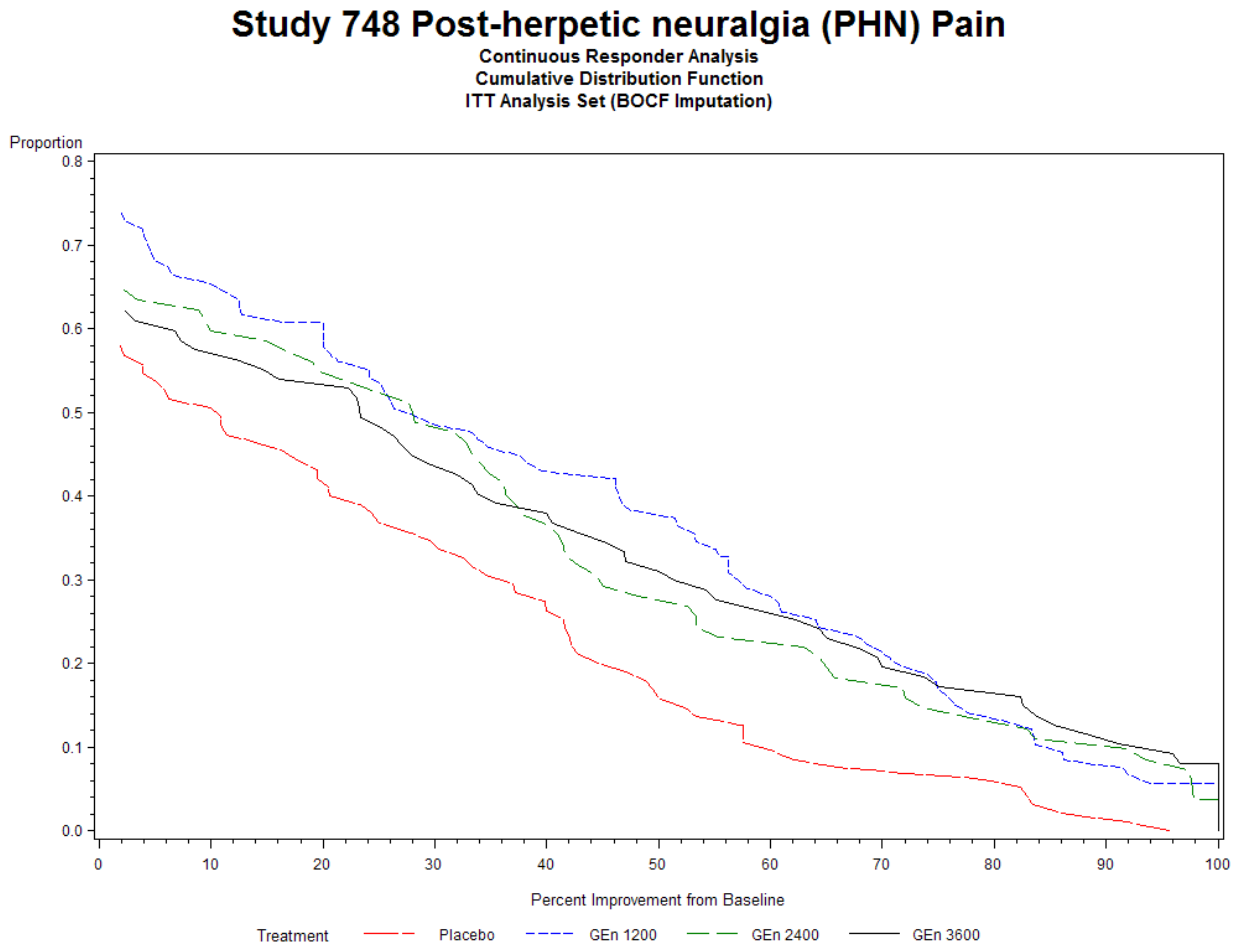
The applicant had done analyses using data sets with four different imputation methods applied. One of those was the Baseline Observation Carried Forward (BOCF) imputation method, in which any missing data at Week 13 was replaced with the baseline value, regardless of the reason for missing data. In terms of the change from baseline or percent change from baseline outcomes, this resulted in a value of zero. For the continuous responder analysis, I used data on discontinuation status to classify non-responders. Patients who did not discontinue **but reported worsening pain** were also classified as non-responders. In Table 5 and Figure 2 of my review, the category labeled ≥0% only included the proportion of subjects that did not withdraw from the study and did not report worsening pain. I have included those results in this addendum as well.

Table 5: Study 748 Responder Analysis: Change in 24-hour Average Pain Intensity from Baseline to Week 13 (Discontinuations coded as Non-responders; ITT; BOCF Imputation)

		Percent Improvement From Baseline									
Treatment Group	N	≥0% *	≥10%	≥20%	≥30%	≥40%	≥50%	≥60%	≥70%	≥80%	≥90%
Placebo	95	56 59%	48 51%	40 42%	33 35%	26 27%	16 17%	10 11%	7 7%	6 6%	2 2%
GEn 1200	107	80 75%	71 66%	65 61%	52 49%	46 43%	41 38%	31 29%	23 21%	15 14%	9 8%
GEn 2400	82	54 66%	50 61%	45 55%	40 49%	31 38%	23 28%	19 23%	15 18%	11 13%	9 11%
GEn 3600	87	55 63%	50 57%	47 54%	38 44%	34 39%	28 32%	23 26%	18 21%	15 17%	10 11%

* All subjects who discontinued prior to completing treatment for any reason were classified as non-responders.
Source: SAS datasets

Figure 2: Continuous Responder Analysis Curves (ITT; BOCF)



Katherine B. Meaker, M.S.
Mathematical Statistician

Dionne Price, Ph.D.
Team Leader

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/s/

KATHERINE B MEAKER
05/21/2012

DIONNE L PRICE
05/22/2012
concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22399 / 003
Drug Name:	Horizant (gabapentin enacarbil)
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Clinical Team:	Medical Officer: Robert Levin, M.D. Medical Team Leader: Frank Pucino, Pharm.D.
Project Manager:	Sharon Turner-Rinehart

Keywords: NDA Review; Single study

Table of Contents

1. EXECUTIVE SUMMARY

The applicant submitted results from a single randomized, double-blind, placebo-controlled, parallel arm, multicenter clinical study to support the efficacy of gabapentin encarbil (GEn) for the treatment of pain in adults with postherpetic neuralgia (PHN). Three doses of GEn were included in the study: 1200 mg/day, 2400 mg/day, and 3600 mg/day. The applicant is only requesting approval for the 1200 mg/day dose based on the overall efficacy/safety profile.

The single primary endpoint of interest was the change from baseline to Week 12 in the average 24-hour pain intensity score. This was measured in a daily diary using an 11-point scale where 0 denoted no pain and 10 denoted pain as bad as you can imagine. Secondary endpoints included the percent of subjects achieving various levels of reduction in average 24-hour pain intensity, the amount of rescue medication used, and patient global impression of change. In all the analyses, each of the three doses of GEn was compared to placebo, with a Dunnett's adjustment for multiplicity. There were no comparisons planned between the GEn dose groups.

All three doses of GEn were statistically better than placebo for the primary and secondary endpoints. There is sufficient evidence to support the efficacy of GEn 1200 mg/day for the treatment of adults with pain due to postherpetic neuralgia.

2. INTRODUCTION

Gabapentin encarbil (GEn) was approved for Restless Legs Syndrome (RLS) on April 6, 2011. It was granted orphan-drug status for the management of postherpetic neuralgia on June 7, 2011.

Postherpetic neuralgia is a peripheral neuropathic pain syndrome which may occur after an episode of varicella-zoster virus (shingles), with pain persisting more than 3 months after the rash and blisters have healed. PHN causes pain and discomfort on the skin.

2.1 Overview

The pre-sNDA meeting was held on March 17, 2011 to discuss this supplemental NDA submission. Two key statistical issues discussed at that meeting were the imputation method to be used, and the applicant's proposal to not combine data from three efficacy studies due to differing study designs. It was agreed that only one principal efficacy study would be required in the context of a 505(b)(2) application if it could be demonstrated that the active drug in the systemic circulation was gabapentin and not gabapentin encarbil (the prodrug). The applicant provided clinical pharmacology studies to support that position, and the clinical team concurred at the filing meeting.

Details of the three efficacy studies in PHN patients are provided in Table 1. The desired study design for the PHN indication is a 12-week, parallel group, placebo-controlled superiority study. Study PXN110748 is considered the single study adequately designed to provide efficacy data to support this indication. Study PXN110527 was a crossover study with no placebo control group, with only 28 days on each treatment. In study XP009/PXN111044 all patients were on Neurontin® prior to and during treatment with GEn, and patients received GEn treatment for only 2 weeks. We agreed that the studies did not need to be combined in presentation of efficacy for this application.

Table 1: Studies of gabapentin encarbil (GEn) in Patients with PHN

Study Identifier	Study Objective(s)	Study Design	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects (enrolled)
NA / PXN110748	Efficacy and safety	R, DB, PC, Parallel group	GEn 600 mg, 1200 mg, or 1800 mg BID; Oral; 1 week titration, 12 weeks maintenance, and 1 week taper	376
NA / PXN110527	Efficacy, safety, and dose-response	R, DB, PC, Crossover	GEn 600 mg or 1800 mg BID; Oral; 28 days, then XO (all subjects take 1200 mg BID x 4 days) followed by 28 days	138
XP009 / PXN111044	Efficacy, safety, and PK in post-herpetic neuralgia	R, DB, PC, Parallel group	Neurontin® 600 mg TID followed by a double-blind period with either GEn 1200 mg BID or placebo; Oral; 11 days plus 14 days	115

Source: Meeting Briefing Document Table 20.

At the time of the pre-sNDA meeting, the studies in patients with PHN had already been completed and the data unblinded. The analysis planned in the protocol used a last observation carried forward (LOCF) imputation for missing data. The applicant also proposed to provide results using a more conservative imputation approach, baseline observation carried forward (BOCF). The following is the specific question and response pertaining to missing data.

> **Question 29:** For each of the PHN studies (PXN110748, XP009, and PXN110527), the primary efficacy analysis of the primary endpoint was based on a dataset that used LOCF as the imputation method. As further supportive evidence, the results of an analysis of the primary endpoint using BOCF as the imputation method will be provided for each individual study. Does the Agency concur with GSK's proposal to provide results of a BOCF analysis only for the primary efficacy endpoint for each study (PXN110748, XP009, and PXN110527)?
>
> **FDA Response**
> Your studies have been completed, unblinded, and analyzed. Thus, our advice regarding

analyses is limited. However, you should be aware of the following.

Over the past several years, the Division has not accepted the last observation carried forward (LOCF) imputation strategy for pain trials. In such trials, patients may discontinue from the study because of a bad outcome such as intolerable side effects resulting from the study treatment. Consequently, the LOCF approach may result in a good score being assigned to a bad outcome. Thus, we have recommended use of a conservative strategy that appropriately addresses this concern. Recently, the National Academy of Sciences (NAS) released a report on missing data (http://www nap.edu/catalog.php?record_id=12955) that does not favor single imputation strategies unless the assumptions that underlie the imputations are scientifically justified.

For your completed studies, an analysis utilizing a BOCF approach has one feature which we continue to favor in that it attributes poor outcomes to those patients who discontinue early. You should provide results of the BOCF analyses for endpoints for which you may potentially desire label claims.

2.2 Data Sources

Study reports and the ISE were provided electronically as Adobe Acrobat .pdf files, and were accessible in the electronic data room (edr):
\\Cdsesub1\evsprod\NDA022399\0056\m5\53-clin-stud-rep\535-rep-effic-safety-stud

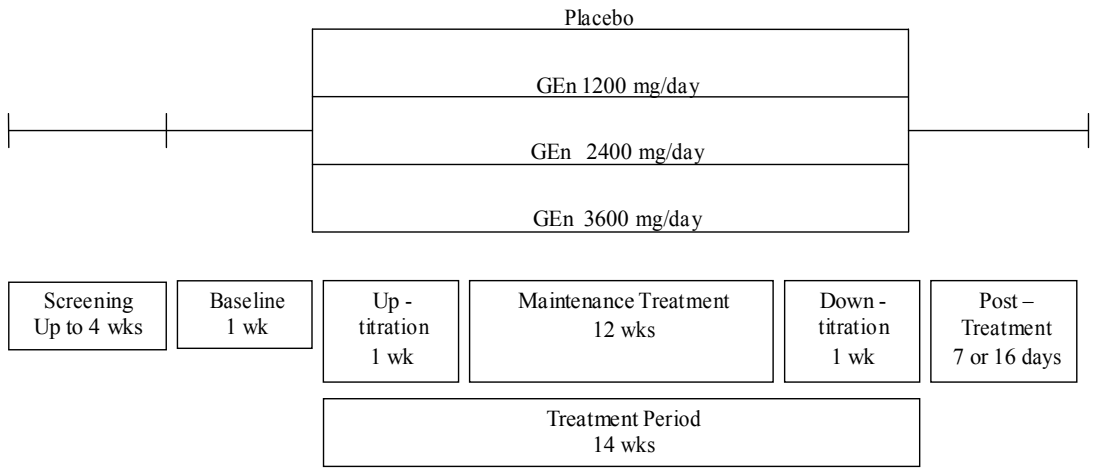
Data was provided in SAS datasets which were well-organized and clearly documented but not CDSIC-compliant. SAS program files to support the analyses presented in the Integrated Summary of Efficacy (ISE) section of the supplement were also provided electronically. The link to the data is:
\\Cdsesub1\evsprod\NDA022399\0056\m5\datasets\pxn110748\analysis\datasets

3. STATISTICAL EVALUATION

Study PXN 110748 (conducted 2/08 – 7/09)

This is a randomized, double-blind, placebo-controlled, parallel arm, multicenter study. It was conducted at 72 sites in the United States and Canada. The primary objective was to investigate the efficacy of GEn to reduce pain in patients with neuropathic pain associated with PHN. Patients were adults who were diagnosed with PHN at least 3 months prior to screening, and reported a baseline 24-hour average pain intensity score of at least 4 on a 0—10 Pain Intensity Numerical Rating Scale (Pain-NRS).

Figure 1: Study Design Diagram (Study 748)



Source: Clinical Study Report Figure 1.

After eligibility was determined during screening and baseline periods, patients were randomly assigned, using a 1:1:1:1 ratio, to one of the four treatment arms. Patients received double-blind treatment for a total of 14 weeks including a 1-week up-titration, 12 weeks on the fixed maintenance dose, and a 1-week down-titration. The primary focus for the efficacy evaluation was the maintenance treatment period, specifically the landmark analysis at Week 12 of the maintenance period.

3.1 Data and Analysis Quality

The applicant included clear documentation for all data sets (raw and analysis), along with a Reporting and Analysis Plan (RAP) providing additional details on data manipulation used to prepare the Clinical Study Report (CSR). I was able to reproduce all analyses presented by the applicant and to conduct additional analyses.

3.2 Evaluation of Efficacy

Study Design and Endpoints

The primary endpoint was the change from baseline in the 24-hour average pain intensity. Pain intensity was recorded in a daily diary and measured on an 11-point Numerical Rating Scale anchored by 0 representing no pain and 10 representing pain as bad as you can imagine. This was analyzed as the mean change and as the percent of patients who achieved various levels of improvement.

Other endpoints of interest to the medical reviewer, Dr. Levin, were the Patient Global Impression of Change and the amount of rescue medication used. Additional secondary endpoints presented by the applicant were the average pain during daytime and nighttime,

worst pain during daytime and nighttime, pain upon waking, pain at bedtime, sleep interference, and clinician global impression of change. Only the results of the primary endpoint are presented in the label, so there was no plan to adjust for multiplicity for secondary endpoints.

Patient Disposition, Demographic and Baseline Characteristics

A total of 376 patients were enrolled in Study 748. Randomization was stratified within center and numerous centers randomized less than eight participants, which resulted in uneven randomization across the four treatment arms. Each treatment arm did have at least the minimum number of subjects (n=82) planned in the power calculations. As shown in Table 2, the main difference in drop outs across the groups was that there was a higher rate due to lack of efficacy in the placebo groups, and higher rate due to adverse events in the higher doses of gabapentin encarbil. Neither of these was unexpected.

Table 2: Patient Disposition (Study 748)

	Placebo	Gabapentin encarbil GEn 1200mg	Gabapentin encarbil GEn 2400mg	Gabapentin encarbil GEn 3600mg
Randomized	95	107	84	90
Received Treatment = Intent-to-Treat (ITT)	95 (100%)	107 (100%)	82 (100%)	87 (100%)
Completed up-titration phase	89 (94%)	103 (96%)	79 (96%)	81 (93%)
Completed maintenance phase	65 (67%)	87 (79%)	61 (73%)	57 (64%)
Reason for Discontinuation during Titration Phase:	6 (6%)	4 (4%)	5 (6%)	9 (10%)
Adverse event	4 (4%)	3 (3%)	3 (4%)	3 (3%)
Lack of efficacy	0	0	0	1 (1%)
Subject withdrew consent	0	1 (1%)	0	1 (1%)
Protocol Deviation	2 (2%)	0	1 (1%)	4 (5%)
Investigator discretion	0	0	1 (1%)	0
Reason for Discontinuation during Maintenance Phase:	24 (25%)	16 (15%)	18 (22%)	24 (28%)
Adverse event	7 (7%)	3 (3%)	9 (11%)	13 (15%)
Lack of efficacy	6 (6%)	1 (1%)	1 (1%)	3 (3%)
Subject withdrew consent	5 (5%)	5 (5%)	4 (5%)	3 (3%)
Protocol Deviation	3 (3%)	3 (3%)	3 (4%)	4 (4%)
Investigator discretion	2 (2%)	2 (2%)	1 (1%)	0
Lost to follow-up	1 (1%)	2 (2%)	0	1 (1%)
Discontinued after maintenance phase	1 (1%)	2 (2%)	1 (1%)	1 (1%)

Source: Clinical Study Report Table 8 and SAS datasets

As shown in Table 3, the four treatment groups were balanced across demographic and baseline characteristics.

Table 3: Summary of Demographic and Baseline Characteristics (Study 748)

	Placebo N=95	**GEn 1200 mg N=107**	**GEn 2400 mg N=82**	**GEn 3600 mg N=87**	**Total N=371**
Age (y)					
Mean (SD)	61.7 (12.77)	61.7 (12.58)	64.1 (8.94)	61.3 (15.41)	62.1 (12.67)
Median	64.0	65.0	65.0	63.0	64.0
Range	18 – 83	18 – 87	21 – 83	20 – 92	18 – 92
Age Group, n (%)					
≤65 yrs	53 (56)	62 (58)	47 (57)	47 (54)	209 (56)
>65 yrs	42 (44)	45 (42)	35 (43)	40 (46)	162 (44)
Gender, n (%)					
Female	45 (47)	54 (50)	35 (43)	48 (55)	182 (49)
Male	50 (53)	53 (50)	47 (57)	39 (45)	189 (51)
Ethnicity, n (%)					
Hispanic/Latino	13 (14)	10 (9)	7 (9)	9 (10)	39 (11)
Not Hispanic/Latino	82 (86)	97 (91)	75 (91)	78 (90)	332 (89)
Race, n (%)					
White	79 (84)	94 (89)	69 (85)	73 (84)	315 (86)
African American/African Heritage	14 (15)	11 (10)	8 (10)	11 (13)	44 (12)
American Indian or Alaska	0	0	2 (2)	1 (1)	3 (<1)
Asian	1 (1)	1 (<1)	2 (2)	1 (1)	5 (1)
Japanese/East Asian Heritage/South East Asian Heritage	0	1 (<1)	1 (1)	1 (1)	3 (<1)
Central/South Asian Heritage	1 (1)	0	1 (1)	0	2 (<1)
Native Hawaiian or other Pacific Islander	0	0	0	1 (1)	1 (<1)
BMI (kg/m^2), n (%)					
≤30	57 (60)	62 (58)	46 (57)	56 (64)	221 (60)
>30	38 (40)	45 (42)	35 (43)	31 (36)	149 (40)
Baseline 24-hour average pain score, n (%)					
4 - <6.5	56 (59)	63 (59)	58 (71)	47 (54)	224 (60)
6.5 - 10	39 (41)	44 (41)	24 (29)	40 (46)	147 (40)
Baseline 24-hour average pain score					
Mean (SD)	6.33 (1.370)	6.28 (1.525)	5.98 (1.569)	6.47 (1.579)	NA
Range	4.1 – 9.4	4.0 – 10	4.0 – 9.8	4.0 – 10.0	NA

Data Source: CSR PXN110748, Table 1.11, Table 1.13, Table 2.1
NA=Not applicable

Statistical Methodologies

For the primary outcome, the mean score of the daily 24-hour average pain intensity scores was calculated for baseline and each week on treatment. The primary endpoint was the change from baseline to the end of treatment (randomized fixed dose, prior to down-titration). This was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, center, baseline pain, and body mass index (BMI). Each of the dose groups randomized to GEn was compared to placebo, with a Dunnett's test to maintain the overall alpha level at 0.05. This approach is acceptable for this endpoint. The analyses were performed on the intent-to-treat population defined as all randomized patients who received at least one dose of study treatment and who had at least one post-baseline assessment.

The applicant planned in the protocol (section 8.3.2) to use the LOCF approach for missing data, as described here:

> *The primary data set of interest for all efficacy analyses will be the last observation carried forward (LOCF) data set. As such, the primary endpoint, the mean 24-hour average pain intensity score for the last week of treatment, is calculated as the mean of the daily scores for the 7 days prior to the last completed diary entry of the treatment period.*
>
> *For secondary analyses of pain intensity by week, the mean score for each treatment week will be the mean of the non-missing daily scores provided. If no pain intensity data is provided for a given week, that week's mean pain intensity score will be considered missing, and the last non-missing post-baseline pain intensity score recorded for a prior week will be analyzed.*

The appropriate imputation methods for a chronic pain study were discussed at the pre-sNDA meeting. In particular, we explained the concern that good outcomes could be imputed for patients who discontinued due to adverse events. At that meeting, the applicant stated that results for the efficacy analyses using a BOCF approach would also be provided. This is described below in the RAP:

> *For the end of maintenance treatment time point, at which the primary endpoint is analyzed, if a subject withdrew prior to completion of the maintenance treatment period, the mean baseline score will be analyzed. If the subject completed the maintenance treatment period, his last 7 days on maintenance treatment will be analyzed, using the baseline mean for imputation if necessary.*

Analyses using a combination of BOCF and LOCF, referred to as the Hybrid BOCF/LOCF, were provided in the application. If a patient discontinued due to an adverse event, the Baseline value was imputed to any missing weeks on treatment. If a patient discontinued for any other reason, LOCF was used to replace missing values.

In addition to the analyses provided by the applicant, I performed a continuous responder analysis, in which all patients who discontinue were classified as non-responders. For patients who completed the maintenance treatment period, the BOCF imputation was applied.

Results and Conclusions

The results for the primary efficacy endpoint are presented in Table 4. The applicant had planned a LOCF imputation strategy for the primary analysis conducted an analysis using a BOCF imputation strategy as an alternative. The results of the Hybrid BOCF/LOCF imputation and the Observed Cases analyses are also shown. The results of all four imputation methods are consistent and support the efficacy of the GEn 1200 mg/day dose.

The applicant proposed to include the results of the primary endpoint in the label in the form of a graph showing the percent of patients who had achieved at least certain levels of improvement: ≥0%, ≥10%, ≥20%... ≥90%. The results provided by the applicant used BOCF imputation, which assigned all patients who dropped out to the ≥0% improvement category. I reanalyzed the data, classifying all drop outs as non-responders such that the category labeled ≥0% only included the proportion of subjects that did not withdraw from the study and did not report worsening pain. The results of my reanalysis are shown in Table 5 and Figure 2. The results are consistent with the ANCOVA analyses in showing evidence to support the efficacy of the 1200 mg/day GEn dose.

Table 4: Change from Baseline in Mean 24-hour Average Pain Intensity Score to Week 13

	Placebo N=95	GEn 1200 mg N=107	GEn 2400 mg N=82	GEn 3600 mg N=87
Baseline				
n	95	107	82	87
Mean (SD)	6.33 (1.370)	6.28 (1.525)	5.98 (1.569)	6.47 (1.579)
Change from Baseline to Week 13 (LOCF)				
n	95	106	80	87
Adjusted Mean (SE)[1]	-1.66 (0.216)	-2.47 (0.204)	-2.36 (0.237)	-2.72 (0.227)
Adjusted Mean Difference vs. Placebo[2]		-0.81	-0.70	-1.07
95% CI		(-1.40, -0.23)	(-1.33, -0.07)	(-1.68, -0.45)
p-value Adjusted for Multiplicity[3]		0.013	0.029	0.002
Unadjusted p-value[4]		0.007	0.029	0.001
Change from Baseline to Week 13 (BOCF)				
n	95	107	81	87
Adjusted Mean (SE)[1]	-1.32 (0.213)	-2.25 (0.200)	-1.97 (0.232)	-2.00 (0.223)
Adjusted Mean Difference vs. Placebo[2]		-0.94	-0.65	-0.68
95% CI		(-1.51, -0.36)	(-1.27, -0.03)	(-1.28, -0.08)
Unadjusted p-value[4]		0.001	0.040	0.027
Change from Baseline to Week 13 (Hybrid BOCF/LOCF)				
n	95	107	81	87
Adjusted Mean (SE)[1]	-1.59 (.220)	-2.33 (.207)	-2.10 (.240)	-2.24 (.231)
Adjusted Mean Difference vs. Placebo[2]		-0.74	-0.51	-0.65
95% CI		(-1.33,-0.15)	(-1.14, 0.13)	(-1.27, -0.03)
Unadjusted p-value[4]		0.014	0.119	0.040
Change from Baseline to Week 13 (Observed Cases)				
n	94	103	80	86
Adjusted Mean (SE)[1]	-1.64 (.218)	-2.50 (.208)	-2.36 (.238)	-2.72 (.228)
Adjusted Mean Difference vs. Placebo[2]		-0.86	-0.72	-1.08
95% CI		(-1.45, -0.27)	(-1.35, -0.09)	(-1.70, -0.47)
Unadjusted p-value[4]		0.004	0.025	0.001

Data Source: Table 2.3, Table 2.9. Table 2.13, Table 2.17

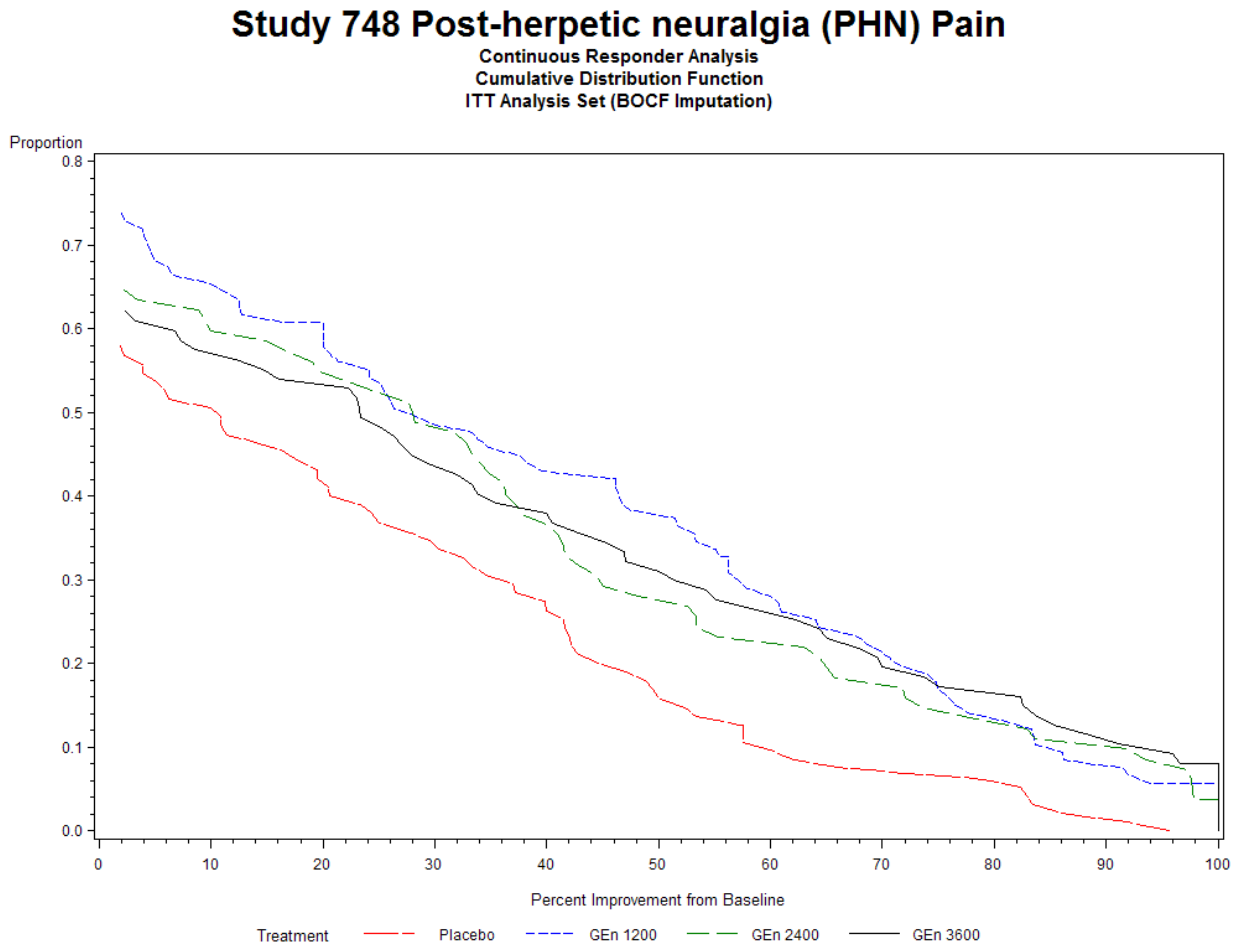
1. The Adjusted Mean and SE are based on an ANCOVA model adjusted for BMI, baseline 24-hour average pain intensity and grouped center.
2. A negative treatment difference indicates benefit, relative to placebo.
3. Adjustments to p-values were made based on multiple treatment arms compared vs. placebo. A step-down procedure that uses Dunnett's test within a closed testing scheme for multiple comparisons with a common control was used to maintain the overall experiment-wise alpha level of 0.05 for the comparisons of GEn vs. placebo.
4. Unadjusted p-values are provided for descriptive purposes, and were not adjusted for multiple comparisons.

Table 5: Study 748 Responder Analysis: Change in 24-hour Average Pain Intensity from Baseline to Week 13 (Discontinuations coded as Non-responders; ITT; BOCF Imputation)

		Percent Improvement From Baseline									
Treatment Group	N	≥0% *	≥10%	≥20%	≥30%	≥40%	≥50%	≥60%	≥70%	≥80%	≥90%
Placebo	95	56 59%	48 51%	40 42%	33 35%	26 27%	16 17%	10 11%	7 7%	6 6%	2 2%
GEn 1200	107	80 75%	71 66%	65 61%	52 49%	46 43%	41 38%	31 29%	23 21%	15 14%	9 8%
GEn 2400	82	54 66%	50 61%	45 55%	40 49%	31 38%	23 28%	19 23%	15 18%	11 13%	9 11%
GEn 3600	87	55 63%	50 57%	47 54%	38 44%	34 39%	28 32%	23 26%	18 21%	15 17%	10 11%

* All subjects who discontinued prior to completing treatment for any reason were classified as non-responders. This category only includes the percentage of subjects that completed the study and had no worsening of pain.
Source: SAS datasets

Figure 2: Continuous Responder Analysis Curves (ITT; BOCF)



Results of the Van der Waerden Overall and Two-Sample Tests confirmed that the distribution of the placebo group was statistically significantly different from those of the three GEn groups (p-values: 0.016 overall test; <0.01 Placebo vs. GEn1200 mg; <0.04 placebo vs. GEn 2400 mg; <0.04 placebo vs. GEn 3600 mg)

Dr. Levin requested that I analyze two additional secondary endpoints of interest. These are shown in Table 6. The results are consistent with GEn 1200 mg/day being more efficacious than placebo, although it is not appropriate to conduct tests of statistical significance for secondary endpoints.

Table 6: Secondary Endpoints (ITT, LOCF)

	Placebo N=95	GEn 1200 mg N=107	GEn 2400 mg N=82	GEn 3600 mg N=87
Mean Daily Dosage of Rescue Medication (mg)				
N	95	106	80	87
Adj mean change[1]	-41.00	-289.94	-260.03	-266.21
SE	89.49	84.35	97.85	93.50
Treatment diff. vs. Placebo [2]	-	-248.93	-219.03	-225.20
95% CI	-	(-490.5, -7.33)	(-479.8, 41.77)	(-479.0, 28.60)
Patient Global Impression of Change				
Number Non-missing	85	103	78	76
Improved (Much or Very Much)	24 (28%)	45 (44%)	35 (45%)	39 (51%)
Minimal or No Change	54 (63%)	53 (51%)	41 (53%)	34 (44%)
Worsened	7 (8%)	5 (5%)	2 (3%)	3 (4%)

Data Source: Clinical Study Report Table 2.53 and 2.81; SAS datasets
[1] A negative treatment difference indicates benefit, relative to placebo.
[2] Adjusted mean, SE and 95% CI are based on an ANCOVA model with BMI, baseline mean daily dose of rescue medication, and grouped center, and treatment as terms in the model.

There were no statistical issues aside from the imputation method to be used. All the results are consistent and show supportive evidence for the efficacy of the GEn 1200 mg/day dose.

3.3 Evaluation of Safety

The evaluation of safety data was conducted by Dr. Levin. Dr. Levin did not identify any unexpected adverse effects and found the safety profile to be comparable with that seen in the PHN population. No additional review of safety endpoints was requested by Dr Levin, and the reader is referred to Dr. Levin's review for detailed information regarding the adverse event profile

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age

Subgroup analyses by gender, race, and age group are shown in Table 7. Study 748 was conducted in North America, so an analysis by geographic subgroup was not done.

There were no noteworthy differences among the groups for gender and age. In the analysis by race, the mean change in the Non-Caucasian subgroup was numerically larger in the placebo group than in the GEn 1200 mg/day group, but the sample sizes in the Non-Caucasian subgroup were small (≤16 per arm). I evaluated graphs of the observations and found no pattern or trend to indicate this finding was meaningful. The results for the Non-Caucasian subgroup in the higher two GEn dose groups were in the expected direction.

Table 7: Subgroup Analyses (ITT; BOCF)

	Placebo N=95		GEn 1200 mg N=107		GEn 2400 mg N=82		GEn 3600 mg N=87	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Gender								
Female	45	-1.34 (1.73)	54	-2.85 (2.57)	35	-1.93 (2.03)	48	-2.18 (2.18)
Male	50	-1.30 (1.67)	53	-1.61 (1.87)	47	-1.92 (2.00)	39	-1.91 (2.31)
Race								
Caucasian	79	-1.12 (1.69)	94	-2.46 (2.37)	69	-1.74 (2.00)	72	-2.09 (2.23)
Non-Caucasian	16	-2.29 (1.36)	13	-0.62 (0.98)	13	-2.89 (1.75)	15	-1.90 (2.28)
Age Group								
≤ 65 years	53	-1.65 (1.77)	62	-2.27 (2.47)	47	-2.09 (2.07)	47	-2.05 (2.07)
Over 65 years	42	-0.90 (1.49)	45	-2.20 (2.13)	35	-1.70 (1.91)	40	-2.06 (2.43)

Source: SAS datasets

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This application included one randomized, double-blind, placebo-controlled, parallel arm, multicenter study conducted in the United States and Canada. The study was conducted according to the protocol. The initial planned analysis used a LOCF imputation strategy which is not an appropriate method to handle missing data in a chronic pain study. Additional analyses with alternative imputations were all consistent.

5.2 Comments on Label

The results presented by the applicant in the proposed label [redacted] (b) (4)

Two statements are included in the gabapentin encarbil label that are similar to statements in labels of approved products for the same indication. The clinical studies included to support the treatment of the PHN indication in approved labels were similar in design to Study 748 to support gabapentin encarbil in this application. These endpoints are derived from the primary endpoint but were not pre-specified as being intended for the label. The clinical team in DAAAP determined they were clinically relevant to include. I confirmed the statistical significance of the two outcomes. The proposed label text is shown below, with the two statements underlined:

> *Treatment with HORIZANT statistically significantly reduced the mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline at all doses tested. A benefit over placebo was observed for all 3 doses of HORIZANT as early as Week 1 and maintained to the end of treatment. Additional benefit of using doses of greater than 1,200 mg a day was not demonstrated.*
>
> *For various degrees of improvement in pain from baseline to end of maintenance treatment, Figure 2 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%.*

5.3 Conclusions and Recommendations

There is sufficient evidence provide by Study 748 to support the efficacy of the GEn1200 mg/day dose for the treatment of pain associated with postherpetic neuralgia. All results were consistent in support of this conclusion.

Signatures/Distribution List Page

Katherine B. Meaker, M.S.
Mathematical Statistician

Dionne Price, Ph.D.
Team Leader

Thomas Permutt, Ph.D.
Division Director

CHECK LIST

Number of Pivotal Studies: 1

Trial Specification

Specify for each trial:

Protocol Number (s): PXN110748
Protocol Title (optional): An efficacy and safety study of gabapentin encarbil compared with a concurrent placebo control in subjects with neuropathic pain associated with post-herpetic neuralgia (PHN)
Phase: 3
Control: Placebo Control
Blinding: Double-Blind
Number of Centers: 72
Region(s) (Country): US (87%), Canada (13%)
Duration: 14 weeks
Treatment Arms: Placebo/ GEn 1200 mg / GEn 2400 mg / GEn 3600 mg
Treatment Schedule: 600mg administered orally twice daily (b.i.d.); 1200 mg b.i.d; 1800 mg b.i.d.
Randomization: Yes
Ratio: 1:1:1:1
Method of Randomization: stratified by site
Primary Endpoint: change from baseline to Week 12 on the mean average pain intensity score
Primary Analysis Population: ITT
Statistical Design: Superiority
Adaptive Design: No
Primary Statistical Methodology: ANCOVA
Interim Analysis: No
Sample Size: 92 per trmt arm; 368 total planned enrollment
Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes

Statistic = T-test (with Dunnett's adjustment**)**
Power= 90%
Δ= 1.2 treatment difference (std. dev. = 2.1)
α = 0.05

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation? no
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? no
- Were the **Covariates** pre-specified in the protocol? yes
- Did the Applicant perform **Sensitivity Analyses**? yes
- How were the **Missing Data** handled? In protocol planned LOCF; At preNDA meeting applicant agreed to submit BOCF as well; also provided Hybrid BODF/LOCF and Completers analyses.

- Was there a **Multiplicity** involved? yes

  If yes,

  Multiple Arms (Yes/No)? yes

  Multiple Endpoints (Yes/No)? no

  Which method was used to control for type I error? Dunnett's
- **Multiple Secondary Endpoints**: Are they being included in the label? No

  If yes, method to control for type 1 error.

Were Subgroup Analyses Performed (Yes/No)? yes

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? no
- Overall, was the study positive (Yes/No)? yes

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

/s/

KATHERINE B MEAKER
05/09/2012

DIONNE L PRICE
05/10/2012
concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-399/S-003

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY Amendment

NDA: 22399 S3	Submission Date(s): August 9, 2011; November 8, 2011; December 21, 2011
Proposed Brand Name	Horizant Extended Release (ER) tablets
Generic Name	Gabapentin enacarbil (GEn)
Reviewer	Li Zhang, Ph.D.
Pharmacometric TL	Atul Bhattaram, Ph.D.
OCP Team Leader	Yun Xu, Ph.D.
OND division	DAAAP
Sponsor	GSK
Submission Type	505(b)(2), Efficacy Supplement
Formulation; Strength(s)	Extended Release Oral Tablet; 300 and 600 mg
Dosing regimen	600 mg in the morning for 3 days, increased to 600 mg BID on day 4
Indication	Management of Postherpetic Neuralgia (PHN)

FDA clinical pharmacology review for sNDA 22399/003 (darrts on May 3, 2012) mentioned that "HORIZANT® should not be recommended for End-Stage Renal Disease (ESRD) patients given the fact that ESRD subjects will have varying dialysis times, and potentially varying HORIZANT dosing schedules, there is no dosing and dialysis scenario that is practically possible that would provide a profile in all ESRD subjects that never exceeds the exposures in normal subjects. To be consistent with clinical pharmacology review for RLS patients, HORIZANT dosing is therefore not recommended in subjects with ESRD and on dialysis for PHN patients".

While on May 14, 2012, sponsor sent response to label edits and explained that "GSK inadvertently did not distinguish between the RLS and PHN dosing recommendations for patients on hemodialysis in our 16 January 2012 amendment after the revision to the RLS dosing recommendation in hemodialysis was approved (Dec 2011). As RLS symptoms occur predominantly in the evening/night, dosing of HORIZANT is recommended in the evening such that the maximal drug concentrations occur in the evening/night. Due to the lack of renal function to clear gabapentin, patients requiring dialysis have a sustained concentration day and night except during the dialysis session when the concentration declines rapidly. Patients with RLS need therapeutic concentration during the evening/night; therefore HORIZANT is not recommended for RLS patients with ESRD receiving hemodialysis. However, patients with PHN need sustained therapeutic concentration day and night. The profile of concentrations with twice

daily dosing in the treatment of PHN support reduced dosing in patients with PHN and on hemodialysis."

Reviewer Comments

Based on the differences in two disease conditions, PHN patients may need to maintain therapeutic concentration during day and night. As mentioned in original clinical pharm review, based on simulations, 300 mg following every dialysis would allow ESRD patients with 1% or less normal CL/F to achieve concentrations comparable to the reference range (60-120 mL/min), and the concentrations in subjects with 5% or more normal CL/F to be at the lower end of the reference range. Therefore, sponsor's proposed dosing guidelines **"300 mg following every dialysis. Increase to 600 mg following every dialysis if needed"** for patients with CRCL <15 mL/min on hemodialysis is acceptable.

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/s/

LI ZHANG
05/17/2012

VENKATESH A BHATTARAM
05/17/2012

YUN XU
05/17/2012

CLINICAL PHARMACOLOGY REVIEW

NDA: 22399 S3	Submission Date(s): August 9, 2011; November 8, 2011; December 21, 2011
Proposed Brand Name	Horizant Extended Release (ER) tablets
Generic Name	Gabapentin enacarbil (GEn)
Reviewer	Wei Qiu, Ph. D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
Pharmacometric Reviewer	Li Zhang, Ph.D.
Pharmacometric TL	Atul Bhattaram, Ph.D.
OND division	DAAAP
Sponsor	GSK
Relevant IND(s)	IND 68,341
Submission Type	505(b)(2), Efficacy Supplement
Formulation; Strength(s)	Extended Release Oral Tablet; 300 and 600 mg
Dosing regimen	600 mg in the morning for 3 days, increased to 600 mg BID on day 4
Indication	Management of Postherpetic Neuralgia (PHN)

Table of Contents

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the efficacy supplement for NDA 22-399 submitted on August 9, 2011, November 8, 2011, and December 21, 2011 and finds it acceptable from clinical pharmacology perspective.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

The Key clinical pharmacology findings for this sNDA are summarized below:

- Steady state gabapentin exposure at the recommended HORIZANT dose of 1200 mg/day is predicted to be between the gabapentin exposure of Neurontin from 900 mg/day to 1800 mg/day, the recommended therapeutic dose range for Neurontin.
- Blood levels of the pro-drug gabapentin enacarbil are low and transient (≤ 2% of corresponding gabapentin plasma levels).
- Proposed dosing regimen for HORIZANT in Postherpetic Neuralgia patients with varying degrees of renal function is acceptable. However, the proposed dosing guidelines for End-Stage Renal Disease (ESRD) groups of renal impaired patients are not acceptable. Given the fact that ESRD subjects will have varying dialysis times, and potentially varying HORIZANT dosing schedules, there is no

dosing and dialysis scenario that is practically possible that would provide a profile in all ESRD subjects that never exceeds the exposures in normal subjects Thus, this product is not recommended for Postherpetic Neuralgia patients with ESRD.

Horizant (gabapentin enacarbil) ER tablet was approved for the treatment of moderate-to-severe primary Restless Leg Syndrome (RLS) in adults under NDA 22-399 via a 505(b)(1) pathway on April 6, 2011. Sponsor submitted an efficacy supplement to NDA 22-399 for Horizant ER tablets for the management of postherpetic neuralgia (PHN) via a 505(b)(2) pathway. The listed drug is Neurontin (gabapentin) tablet (NDA 20-235). In adults with PHN, Neurontin therapy may be initiated as a single 300-mg dose on Day 1, 600 mg/day on Day 2 (divided BID), and 900 mg/day on Day 3 (divided TID). The dose can subsequently be titrated up as needed for pain relief to a daily dose of 1800 mg (divided TID). For Horizant ER tablets, the proposed dosing regimen is to start at a dose of 600 mg in the morning for 3 days, then increase to 600 mg twice daily beginning on Day 4.

The clinical and clinical pharmacology database for this supplemental NDA consists of 17 clinical pharmacology studies, one population PK/PD, one modeling-simulation for renal impaired patients, and 3 phase II studies. Sixteen clinical pharmacology studies (PK studies XP006, XP018, XP065, XP069, bioavailability studies XP019, XP044, XP057, XP086, food effect studies XP022, XP087, extrinsic factor studies XP067, XP068, intrinsic factor studies XP066, XP072, XP073, thorough QTc stud XP078), and the population PK/PD were submitted in the original NDA for the indication of RLS. The only (b) (4) which was not submitted in the original NDA was (b) (4) , but it was included in the resubmission of the original NDA 22-399 dated October 6, 2010 and was reviewed by the clinical pharmacology reviewer Dr. Seongeun Cho. (b) (4) (b) (4) Modeling-simulation for patients with renal impairment was submitted as a supplement to NDA 22-399 and was used to support dosage adjustments (see pharmacometric review by Dr. Li Zhang). The 3 phase II studies in the management of PHN include principal efficacy study PXN110748 and two supportive studies PXN110527 and XP009. This review focused on Study XP-009

where gabapentin PK was determined. Two published literatures were submitted to support the exposure for Neurontin 300 mg TID.

Relative Exposure to Gabapentin following the Administration of Horizant as Compared to Neurontin®:

The predicted mean steady state Cmax, AUC0-24, and Cmin values of gabapentin at proposed dosing of 600 mg twice daily are 5.5 ug/mL, 97 ug.hr/mL, and 3.30 – 4.36 ug/mL, respectively, which are lower than that for Neurontin 600 mg TID and greater than that for Neurontin 300 mg TID.

For the 42 patients who received both Neurontin and GEn, mean steady state Cmax and AUC0-24hr values of gabapentin were 9.07 ug/mL and 166 ug.hr/mL, respectively, following oral administration of Neurontin 600 mg TID. Following oral administration of GEn 1200 mg BID to the same patients, mean steady state Cmax and AUC0-24hr values of gabapentin were 11.0 ug/mL and 194 ug.hr/mL, respectively. Since gabapentin exposure increases in an approximate dose proportional manner over the dose range of 300 to 6000 mg (see Dr. Ju-Ping Lai's clinical pharmacology review for the original NDA), mean Cmax and AUC0-24hr of gabapentin for GEn 600 mg BID dosage regimen are predicted to be 5.5 ug/mL and 97 ug.hr/mL, respectively. In addition, mean gabapentin trough concentrations following the administration of Neurontin 600 mg TID was 5.20 ug/mL. Gabapentin trough concentrations for GEn 1200 mg BID ranged from 6.61 ug/mL to 8.72 ug/mL. The predicted trough concentrations of gabapentin for GEn 600 mg BID based on dose proportionality are predicted to be from 3.30 – 4.36 ug/mL.

Literature data from two publications showed that the Cmax, AUC0-24hr, and Cmin values of gabapentin given Neurontin 300 mg TID are approximately 4.02 – 4.56 ug/mL, 74.4 – 94.1 ug.hr/mL, and 2.13 ug/mL, respectively.

Gabapentin Enacarbil Plasma Levels in Comparison to Gabapentin following the administration of Horizant:

According to Dr. Ju-Ping's Lai's review, exposure to intact GEn in blood after oral administration of GEn was consistently low (≤ 2% of the corresponding gabapentin

levels) at all dose levels (350 – 288 mg immediate release formulation) under fasting condition as examined in Study XP006. GEn levels were also determined in one PK study using IR formulation 350 mg to 2100 mg BID under fasting condition (XP018) and six PK studies (XP019, XP022, XP067, XP069, XP072, and XP073) using ER formulation given as single dose or multiple doses under fasting or fat conditions with daily dose ranging from 600 mg to 6000 mg. The data obtained from these studies are consistent with Study XP006. The relative exposure ratios (GEn/gabapentin) calculated as the ratio of the molar Cmax and AUC values for the two compounds were ≤ 0.25% and ≤ 1.69%, respectively.

Dosage Adjustment in PHN Patients with Various Degrees of Renal Impairment

The proposed dosing regimen for Horizant® in Postherpetic Neuralgia patients with varying degrees of renal function acceptable is acceptable. However, the proposed dosing guidelines for End-Stage Renal Disease (ESRD) groups of renal impaired patients are not acceptable and Horizant® should not be recommended for ESRD patients.

2 Question Based Review

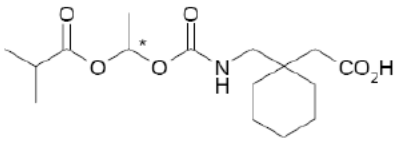
2.1 General Attributes of the Drug

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

Gabapentin enacarbil is a white to off-white crystalline solid with a melting onset of approximately 64^{o}C. The physical-chemical properties of Gabapentin enacarbil is shown in **Table 1**.

Table 1 Physical-Chemical Properties of Gabapentin Enacarbil Drug Substance

Drug Name	Gabapentin Enacarbil
Chemical Name	Cyclohexaneacetic acid, 1-[[[[1-(2-methyl-1-

	oxopropoxy)ethoxy]carbonyl]amino]methyl]
Structure	
Molecular Formula	$C_{16}H_{27}NO_6$
Molecular Weight	329.4
Solubility	0.5 mg/mL in water and 10.2 mg/mL in phosphate buffer (pH 6.3)

The composition of Gabapentin enacarbil ER tablet is shown in **Table 2**.

Table 2 Composition of Gabapentin Enacarbil ER tablets 300 and 600 mg

Component	Quantity (mg/tablet)	
	600 mg	300 mg
(b) (4)		
Gabapentin Enacarbil[1]		(b) (4)
Dibasic Calcium Phosphate Dihydrate[2]		
Talc		
Glyceryl Behenate		
Magnesium Stearate[3]		
Sodium Lauryl Sulfate		
Colloidal Silicon Dioxide		
Ferric Oxide, Red		
(b) (4)		
Sodium Lauryl Sulfate		
Magnesium Stearate[3]		
Total tablet weight (mg)		

Notes:
1. Assuming 100% conversion of GEn to gabapentin in vivo, 600 mg or 300 mg of GEn (MW 329.39) is equivalent to 312 mg or 156 mg of gabapentin (MW 171.24), respectively, on a molecular weight basis.
2. Unmilled or coarse grade
3. Magnesium Stearate is (b) (4)

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

Gabapentin enacarbil is a prodrug of gabapentin and its therapeutic effects are attributable to gabapentin. The exact mechanism of action is unknown but in animal models of analgesia, gabapentin prevents allodynia and hyperalgesia. Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice. Gabapentin also decreases pain-related responses after peripheral inflammation, but

does not alter immediate pain-related behaviors (Please refer to Dr. Emami's pharmacology/toxicology review for more details). Sponsor indicated that the relevance of these models to human pain is not known.

The proposed therapeutic indication is for the management of postherpetic neuralgia in adults.

3. What are the proposed dosage(s) and route(s) of administration?

Gabapentin enacarbil ER tablets are for oral administration. The starting dose is 600 mg in the morning for 3 days, then increase to 600 mg twice daily beginning on Day 4.

2.2 General Clinical Pharmacology

1. What is known about the PK characteristics of HORIZANT (gabapentin enacarbil) in general?

HORIZANT is an extended-release formulation of gabapentin enacarbil, a prodrug of gabapentin. The absorption of gabapentin enacarbil is via an active transport by a proton-linked monocarboxylate transporter, MCT-1, expressed at high levels in the intestinal tract. After oral administration, gabapentin enacarbil undergoes extensive first-pass hydrolysis by non-specific carboxylesterases primarily in enterocytes and to a lesser extent in the liver, to form gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid. Levels of gabapentin enacarbil in blood are low and transient ($\leq$ 2% of corresponding gabapentin plasma levels). The extended exposures to gabapentin increase in an approximate dose-proportional manner over the range of 300 to 6000 mg. Based on urinary recovery of gabapentin, mean bioavailability of gabapentin is from 42% to 65% under fasting condition and about 75% under fed condition. The exposure of gabapentin was increased by 24%, 34%, and 44% by low, moderate, and high fat meals, respectively. The Tmax of gabapentin was 5 hr in fasted subjects and 7.3 hours in fed subjects. Steady state is reached in 2 days with daily administration.

In vitro study showed that the modified release properties of the formulation were compromised in the presence of alcohol, with greater than 60% of the gabapentin

enacarbil dose released within 1 hour at the highest alcohol concentration (40%) (See Dr. Suarez's Review dated October 25, 2011). After reviewing the simulation data for in vivo alcohol effects, it was recommended that the intake of alcohol should be restricted with the use of HORIZANT. The reviewer requested the sponsor submit a labeling supplement to reflect this change in the label (see Dr. Veneeta Tandon's review dated February 29, 2012).

Plasma protein binding of gabapentin is less than 3%. The apparent volume of distribution of gabapentin is 76 L. Gabapentin is not apparently metabolized in humans. Neither gabapentin enacarbil nor gabapentin are substrate, inhibitors, or inducers of the major cytochrome P450 enzymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4). Gabapentin enacarbil is neither a substrate nor an inhibitor of P-glycoprotein in vitro.

Gabapentin is excreted unchanged by the kidney and is believed to involve a component of active secretion via an organic cation transporter (OCT2). The elimination half-life of gabapentin ranges from 5.1 to 6 hr and is unaltered by dose or following multiple dose administration.

There is no gender or age effect on the PK of gabapentin. Apparent oral clearance was significantly decreased from 6.0 to 9.3 L/hr in patients without renal impairment to 4.2 L/hr in moderate and 1.7 L/hr in severe renal impaired patients. Doses of HORIZANT must be adjusted in accordance with renal function. Gabapentin is effectively removed from plasma by hemodialysis. For patients on hemodialysis, treatment with HORIZANT is not recommended. No clinical relevant PK interaction are expected between HORIZANT and substrates of OCT2 (e.g., cimetidine) or MCT-1 (e.g., naproxen).

2. Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetics?

The activity is primarily due to the metabolite, gabapentin. Gabapentin concentrations were measured in all the clinical pharmacology studies and the prodrug gabapentin enacarbil was measured in 8 clinical pharmacology studies.

2.3 Intrinsic Factors

1. What is the pediatric plan?

Gabapentin enacarbil was granted orphan-drug designation for the management of PHN on June 7, 2011. A waiver of the requirement to conduct a pediatric assessment for this indication was granted by the Agency due to the low incidence of PHN in the pediatric population which makes the pediatric studies infeasible at the Pre-NDA meeting dated March 17, 2011.

2. Is the proposed dosing regimen for Horizant in PHN patients with varying degrees of renal function acceptable?

The proposed dosing regimen (**Table 3**) for Gabapentin in Postherpetic Neuralgia patients with varying degrees of renal function acceptable is acceptable. However, the proposed dosing guidelines for End-Stage Renal Disease (ESRD) groups of renal impaired patients are not acceptable and Horizant® should not be recommended for ESRD patients. While for redosing after dialysis, Dr. Veneeta Tandon and Dr. Atul Bhattaram's clinical pharmacology review for the original NDA on 6/24/2011 discussed that although the mean exposure values such as $AUC_{SS,24}$ and $C_{SS,max}$ for gabapentin in these ESRD subjects given HORIZANT after every other dialysis were similar to mean values in normal subjects, the flat profile (two day profile) of exposure in patients on dialysis inevitably departs from the profile in subjects with normal renal function. Given the fact that ESRD subjects will have varying dialysis times, and potentially varying HORIZANT dosing schedules, there is no dosing and dialysis scenario that is practically possible that would provide a profile in all ESRD subjects that never exceeds the exposures in normal subjects. To be consistent with clinical pharmacology review for RLS patients, GEn dosing is therefore not recommended in subjects with ESRD and on dialysis for PHN patients. (See Dr. Li Zhang's pharmacometric review for details).

Table 3 Adjustment of Dosage of HORIZANT for Patients with Postherpetic Neuralgia in Accordance With Creatinine Clearance

Creatinine Clearance (mL/min)	Titration	Maintenance	Tapering
≥60	600 mg in AM for 3 days	600 mg twice daily	600 mg in AM for 1 week
30 – 59	300 mg in AM for 3 days	300 mg twice daily. Increase to 600 mg twice daily as needed[a]	Reduce current maintenance dose to once daily in AM for 1 week
15 – 29	300 mg in AM on Day 1 and Day 3	300 mg in AM. Increase to 300 mg twice daily if needed[a]	If taking 300 mg twice daily, reduce to 300 mg once daily in AM for 1 week. If taking 300 mg once daily, no taper needed.
<15	None	300 mg every other day in AM. Increase to 300 mg once daily in AM if needed[a]	None
~~<15 on hemodialysis~~	~~None~~	~~300 mg following every dialysis. Increase to 600 mg following every dialysis if needed~~[a]	~~None~~

(b) (4)

Based on tolerability and efficacy

2.4 General Biopharmaceutics

1. Is the proposed to-be-marketed formulation the same as the clinical formulation?

The approved original NDA 22-399 for RLS included a 600 mg GEn ER tablet, which was used in all clinical efficacy/safety studies that support the current sNDA (PXN110748, PXN110527, and XP009). A Prior Approval Supplement to register the 300 mg strength was submitted to the Agency on June 24, 2011 (NDA 22-399/S-002, Sequence 62) and was approved by granting a waiver of the requirement for demonstrating vivo bioavailability based on dissolution and CMC data on December 21, 2011. Both 300 mg and 600 mg strengths are the intended commercial formulations for the PHN indication sought for the current sNDA.

2. What is the relative exposure to gabapentin following the administration of proposed therapeutic dose of Horizant in comparison to Neurontin?

The predicted mean steady state Cmax, AUC0-24, and Cmin values of gabapentin at proposed dosing of 600 mg twice daily are 5.5 ug/mL, 97 ug.hr/mL, and 3.30 – 4.36 ug/mL, respectively, which are lower than that at 600 mg TID Neurontin and greater than that at 300 mg TID Neurontin (see **Table 4**).

Sponsor predicted gabapentin steady state PK after dosing of GEn based on Study XP009 assuming dose proportionality and Studies PXN110527, PXN110748, and XP084 based on population PK model. Since rich PK samples were collected in Study XP009, the comparison of gabapentin exposure will be mainly based on the data from this study. For the reference product, Neurontin, the steady state PK data at 600 mg TID was obtained from Study XP009 and the PK data at 300 mg TID were obtained from two published literatures.

Study XP009 is a Phase IIa, multi-center, randomized, double-blind, placebo-controlled efficacy/safety study at a GEn dose of 1200 mg taken every 12 hours (2400 mg/day) in patients with PHN. Patients were 23.0 to 87.2 years of age and had creatinine clearance greater than or equal to 60 mL/min. All enrolled subjects received an initial open-label two-week run-in period on Neurontin. The Neurontin dose was titrated as follows: 300 mg once per day on the first day, 300 mg twice per day on the second day, 300 mg three times per day on the third day, and 600 mg three times a day on the fourth and subsequent days. This was followed by two weeks of treatment with either 1200 mg GEn twice a day or two matching placebo in this second phase of the study. Neurontin or GEn was initially administered without regard to food; however, this was later modified to require administration with food on the day of the PK studies. PK of gabapentin was determined at steady state on the two treatments over the course of one dosing interval (i.e., 8 hrs for Neurontin and 12 hours for GEn). Gabapentin concentration-time profiles are shown in **Figure 1**.

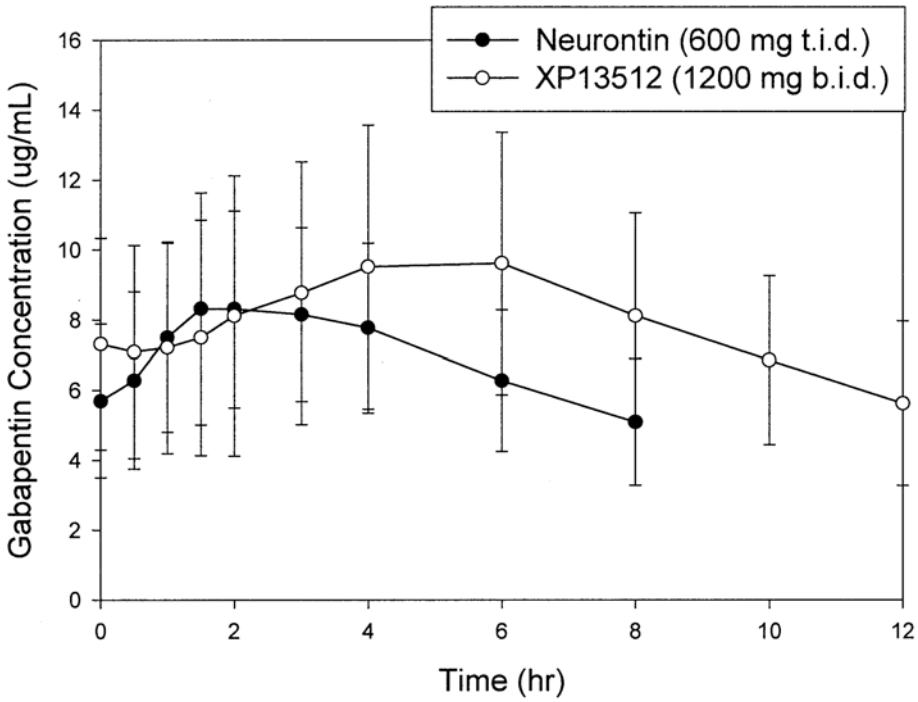


Figure 1 Mean (SD) steady state concentrations of gabapentin in plasma of patients with PHN after repeated oral administration of Neurontin 600 mg TID or GEn (also known as XP13512) 1200 mg BID in Study XP009 (N = 42)

Plasma PK data of gabapentin for a total of 42 patients who received both Neurontin and GEn are shown in **Table 4**. In these patients, following oral administration of Neurontin 600 mg TID, steady state Cmax and AUC0-24hr values were 9.07 ug/mL and 166 ug.hr/mL, respectively. The mean oral bioavailability of gabapentin in these patients was 43% (n = 38). Following oral administration of GEn in the same patients, steady state Cmax and AUC0-24hr values were 11.0 ug/mL and 194 ug.hr/mL, respectively. The mean oral bioavailability of gabapentin in these patients was 77% (n = 38), based on urinary recovery. Gabapentin trough concentrations at the end of Neurontin period in patients who were randomized to GEn treatment had the trough concentration of 5.20 ug/mL. For these patients, gabapentin trough concentrations were also determined on Days of 4, 8, 11 and 14 in randomized treatment period. The mean concentrations ranged from 6.61 to 8.72 ug/mL. Since gabapentin exposure increases in an approximate dose proportional manner over the dose range of 300 to 6000 mg (see Dr. Ju-Ping Lai's clinical pharmacology review for the original NDA submission), Cmax, AUC0-24hr and Cmin are predicted to be 5.5 ug/mL, 97 ug.hr/mL, and 3.30 – 4.36 ug/mL, respectively, following the administration of 600 mg GEn twice daily.

Literature data from two publications showed that the Cmax, AUC0-24hr, and Cmin values of gabapentin given Neurontin 300 mg TID are approximately 4.02 – 4.56 ug/mL, 74.4 – 94.1 ug.hr/mL, and 2.13 ug/mL, respectively.

Thus, the systemic exposure of gabapentin following the administration of GEn 600 mg twice daily would be greater than Neurontin 300 mg TID but less than Neurontin 600 mg TID.

Table 4 Comparison of Gabapentin Mean (%CV) Steady State PK Parameters after Dosing Neurontin and GEn

Parameter	**Study XP-009**[@]					**Bockbrader****	**Hooper*****	
	GEn 1200 mg BID		GEn 600 mg BID	Neurontin 600 mg TID		Neurontin 300 mg TID	Neurontin 300 mg TID	
	n	Mean (%CV)	Mean (%CV)	n	Mean (%CV)	Mean (%CV)	n	Mean (%CV)
Tmax (hr)*	42	4.63* (0, 12)	4.63* (0, 12)	42	2.31* (0, 4)	2.7 (18.0)	12	2.05 (0.95, 4.08)*
Cmax (ug/mL)	42	11.0 (36.3)	5.5 (36.3)	42	9.07 (33.1)	4.02 (23.7)	12	4.56 (23.7)
AUC0-24 (ug.hr/mL)	42	194 (35.9)	97 (35.9)	42	166 (32.5)	74.4 (23.8)	12	94.1 (30.7)
Cmin (ug/mL)	47	6.61-8.72[&]	3.30-4.36	47	5.20 (40)	2.13 (24.5)	NA	
T1/2 (hr)	42	7.37 (40.4)	7.37 (40.4)	32	7.23 (44.5)	5.2	12	5.5 (38.2)

*mean (min, max)

**Bockbrader, H.N. *Clinical Pharmacokinetics of Gabapentin* Drugs of Today1995, 31(8): 613-9.

***Hooper, W.D., M.C. Kavanagh, G.K. Herkes and M.J. Eadie *Lack of a pharmacokinetic interaction between phenobarbitone and gabapentin* British Journal of Clinical Pharmacology 1991, 31: 171-4.

[&]mean values from 4 different visits

@ source data from Tables 11-12, 11-13, End-of-Text Table 6.1

3. What is the relative exposure ratio between gabapentin enacarbil and gabapentin following the administration of gabapentin enacarbil?

According to Dr. Ju-Ping's Lai's review, exposure to intact GEn in blood after oral administration of GEn was consistently low (≤ 2% of the corresponding gabapentin levels) at all dose levels (350 – 2800 mg immediate release formulation) under fasting condition as examined in Study XP006. GEn levels were also determined in one PK study using IR formulation 350 mg to 2100 mg BID under fasting condition (XP018) and six PK studies (XP019, XP022, XP067, XP069, XP072, and XP073) using ER formulation given as single dose (600 mg to 6000 mg) or multiple doses (1200 mg QD,

1200 mg and 1800 mg BID) under fasting or fat conditions. The data obtained from these studies are consistent with Study XP006. The relative exposure ratios for GEn and gabapentin calculated as the ratio of the molar Cmax and AUC values for the two compounds were ≤ 0.25% and ≤ 1.69%, respectively.

Table 5 Mean PK Parameters for GEn and Gabapentin in Blood following Single and Multiple Oral Administration of GEn to Healthy Subjects

Study	Type	N	GEn Dose (mg)	Food	Pharmacokinetic Parameters for GEn in Blood				Pharmacokinetic Parameters for Gabapentin (GP) in Blood				Exposure Ratio (%)[e]	
					C_{max} (µg/mL)	C_{max} (µM)[e]	AUC[a] (µg*h/mL)	AUC (µM*h)	C_{max} (µg/mL)	C_{max} (µM)[d]	AUC[b] (µg*h/mL)	AUC (µM*h)	GEn/GP AUC	GEn/GP C_{max}
XP006	Single Dose (IR)	8	350	Fasted	0.093	0.284	0.065	0.197	3.61	21.1	25.4	148	0.13	1.34
		8	700	Fasted	0.213	0.647	0.198	0.601	6.55	38.3	53.0	310	0.19	1.69
		8	1400	Fasted	0.296	0.899	0.388	1.178	11.30	66.0	85.0	496	0.24	1.36
		8	2100	Fasted	0.316	0.959	0.350	1.063	15.70	91.7	120	701	0.15	1.05
		8	2800	Fasted	0.359	1.09	0.496	1.506	18.10	105.7	162	946	0.16	1.03
XP018	Multiple Dose (IR)	6	350 BID	Fasted	0.052	0.159	0.048	0.146	3.24	18.9	20.0	117	0.12	0.84
		8	700 BID	Fasted	0.177	0.537	0.125	0.379	8.04	47.0	51.2	299	0.13	1.14
		8	1400 BID	Fasted	0.128	0.389	0.114	0.346	14.0	81.8	89.6	523	0.07	0.48
		7	2100 BID	Fasted	0.383	1.163	0.335	1.02	20.7	120.9	128	748	0.14	0.96
XP019	Single Dose (ER)	12	600	Fasted	0.044	0.134	0.104	0.316	2.79	16.30	27.2	159	0.20	0.82
XP022	Single Dose (ER)	12	1200	Fasted	0.040	0.121	0.123	0.373	4.21	24.6	54.5	318	0.12	0.49

[a]AUC_t used for single dose and AUC_{ss} used for multiple dose studies. [b] AUC_{inf} used for single dose and AUC_{ss} used for multiple dose studies. [c] Molecular weight of XP13512 is 329.4 [d] Molecular weight of gabapentin is 171.2 [e] Calculated on a molar basis.

Study	Type	N	GEn Dose (mg)	Food	Pharmacokinetic Parameters for GEn in Blood				Pharmacokinetic Parameters for Gabapentin (GP) in Blood				Exposure Ratio (%)[e]	
					Cmax (µg/mL)	Cmax (µM)[e]	AUC[a] (µg*h/mL)	AUC (µM*h)	Cmax (µg/mL)	Cmax (µM)[d]	AUC[b] (µg*h/mL)	AUC (µM*h)	GEn/GP AUC	GEn/GP Cmax
XP067	Multiple Dose (ER)	11	1200 QD	Mod. Fat	0.045	0.137	0.13	0.392	6.17	36.0	63.3	370	0.11	0.38
		10	1200 QD	Mod.. Fat	0.039	0.118	0.14	0.425	6.52	38.1	71.7	419	0.10	0.31
XP069	Single Dose (ER)	8	2400	Mod. Fat	0.028	0.085	0.094	0.285	11.40	66.6	118	689	0.04	0.13
		8	3600	Mod. Fat	0.050	0.152	0.177	0.537	16.20	94.6	175	1022	0.05	0.16
		8	4800	Mod. Fat	0.083	0.252	0.365	1.108	22.70	132.6	254	1484	0.07	0.19
		8	6000	Mod. Fat	0.136	0.413	0.553	1.679	28.90	168.8	322	1881	0.09	0.24
XP072	Single Dose (ER)	6	600	Fasted	0.060	0.182	0.101	0.307	1.94	11.3	21.0	123	0.25	1.61
		6	1200	Fasted	0.046	0.140	0.150	0.455	4.09	23.9	46.6	272	0.17	0.58
		5	1800	Fasted	0.096	0.291	0.156	0.474	7.04	41.1	67.6	395	0.12	0.71
		5	1800	High Fat	0.031	0.094	0.108	0.328	7.24	42.3	89.5	523	0.06	0.22
XP073	Multiple Dose (ER)	11	1200 BID	Mod. Fat	0.022	0.067	0.074	0.225	8.39	49.0	66.4	388	0.06	0.14
		11	1800 BID	Mod. Fat	0.042	0.128	0.125	0.379	14.40	84.1	106	619	0.06	0.15

[a]AUC_t used for single dose and AUC_{ss} used for multiple dose studies. [b] AUC_{inf} used for single dose and AUC_{ss} used for multiple dose studies. [c] Molecular weight of XP13512 is 329.4 [d] Molecular weight of gabapentin is 171.2 [e] Calculated on a molar basis.

2.5 Analytical Section

1. How is gabapentin measured in the plasma?

Validated methods reviewed in the original NDA were used for the determination of gabapentin in human plasma. The established lower limit of quantitation (LLOQ) was 80 ng/mL for Study XP009 and 50 ng/mL for Studies PXN110748 and PXN110527.

Table 6 Summary of the bioanalytical method for determination of plasma gabapentin concentration

Study	Method	LLOQ	QCs	Accuracy (%Bias)	Precision (%CV)
XP009*	LC-MS/MS	80 ng/mL	150, 1000, 9375, and 100,000 ng/mL	-9.2% to -0.7%	≤ 7.7%
PXN110748**	LC-MS/MS	50 ng/mL	200, 4000, and 40000 ng/mL	-2.4% to 0.5%	≤ 6.3%
PXN110527***	LC-MS/MS	50 ng/mL	200, 4000, and 40000 ng/mL	-1.2% to 1.7%	≤ 5.7%

*Within Study Bioanalytical Report RM2008/00204/00
**Within Study Bioanalytical Report RD2009/01246/00
***Within Study Bioanalytical Report RD2009/01247/00
These reports were submitted on Nov 8, 2011 after the Agency requested the information regarding validation report and within study bioanalytical reports.

3 Detailed Labeling Recommendations

The clinical pharmacology relevant labeling portion includes dosage adjustment for PHN patients with different degrees of renal impairment. Pharmacometric reviewer agrees with sponsor's proposal for patients with creatinine clearance ≥ 60, 30 – 59, 15 - 29, and < 15 mL/min. However, Horizant is not recommended for patients with creatinine clearance less than 15 mL/min and on hemodialysis. Refer to Table 3 in this review for detailed recommendations.

4 Appendix

4.1 Filing memo

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	22-399 S3	Brand Name	Horizant™ ER tablets
OCP Division (I, II, III, IV, V)	II	Generic Name	Gabapentin enacarbil
Medical Division	DARRP	Drug Class	
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	Management of Postherpetic Neuralgia (PHN) in adults
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form	Tablets; 300 and 600 mg
Pharmacometrics Reviewer		Dosing Regimen	600 mg in the morning for 3 days, increased to 600 mg BID (1200 mg/day) on day 4
Date of Submission	August 9, 2011	Route of Administration	Oral
Estimated Due Date of OCP Review	April 2, 2012	Sponsor	GSK
Medical Division Due Date	April 9, 2012	Priority Classification	standard
PDUFA Due Date	June 9, 2012	Relevant INDs	IND 68,341

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	x	1		XP009 (submitted in the original NDA)
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:	x			See above
Phase 3:				
PK/PD -				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Phase 1 and/or 2, proof of concept:	x	2		Studies 110527 & PXN110748
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	x			See above
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		

4.2 Individual Study Synopsis

2. STUDY SYNOPSIS

Name of Company: XenoPort®, Inc.	**Individual Study Table Referring to part of the Dossier** Volume:	**(For National Authority Use Only)**
Name of Finished Product: XP13512 (Transported prodrug of Gabapentin)		
Name of Active Ingredient: Gabapentin	Page:	

Title of Study: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Safety and Efficacy of XP13512 in Patients with Postherpetic Neuralgia	
Investigators: Seventeen Investigators in the United States enrolled patients	
Study Centers: Patients were enrolled at 17 study centers in the United States	
Publication (Reference): None	
Study Period (years): 21 June 2004 to 15 March 2005	**Phase of Development:** Phase 2a

Objectives: The primary objective of the study was to assess the efficacy of XP13512 versus placebo in reducing pain associated with postherpetic neuralgia (PHN). Secondary objectives were to: (1) assess the effects of XP13512 for improvement in sleep, quality of life, and mood; (2) assess gabapentin pharmacokinetics (PK); (3) examine the relationship between gabapentin concentrations produced from XP13512 and treatment response; and (4) assess XP13512 safety and tolerability. Upon review of the efficacy data, an additional objective was identified to determine the efficacy of XP13512 versus Neurontin® in reducing pain associated with PHN.

Rationale for Study Design: This study design enabled the assessment of XP13512 treatment safety and efficacy compared to placebo treatment in patients with PHN. In addition, the study design allowed for assessment of gabapentin PK and concentration-response relationship after administration of Neurontin® and XP13512.

Methodology: This was a multi-center, randomized, double-blind, placebo-controlled, parallel design study assessing the efficacy of XP13512 at a dose of 1200 mg taken every 12 hours in reducing pain associated with PHN. Eligible patients entered in a 7-day baseline period followed by an 11-day Neurontin treatment period. The Neurontin® dose was increased slowly over 4 days to a final dose of 600 mg three times daily (1800 mg/day), which was maintained for an additional 7 days of treatment. At the end of the Neurontin treatment period, patients were randomized to XP13512 1200 mg or placebo given every 12 hours for 14 days. The total planned enrollment was 160 patients entering the Neurontin treatment period in order to obtain 120 evaluable patients (60 per group) in the randomized treatment period.

At the beginning of the study (Day 1), patients underwent routine safety assessments including clinical laboratory tests, vital signs, and electrocardiograms (ECGs). Eligible patients were asked to record their pain score twice daily and morning sleep score once daily for a 7-day baseline period. At the second visit, safety assessments (vital signs and clinical laboratory tests) were performed. Patients also completed Short-Form McGill Pain Questionnaire (SF-MPQ), the Short Form-36 (SF-36), and Profile of Mood States (POMS) assessments. At the end of Visit 2, patients were given Neurontin® 300 mg capsules and dosing instructions. During the Neurontin treatment period, patients continued to record their daily assessments of pain and sleep interference. On Day 19 (Visit 3), patients returned to the clinic for an 8-hour blood and urine PK sample collection. Also during Visit 3, safety assessments (vital signs, ECG, and clinical laboratory tests) were performed. Patients completed the SF-MPQ assessment. At the end of the 8-hour PK evaluation, patients were given their second Neurontin® dose for the day and dispensed two additional Neurontin® capsules to take that evening. Study medication for the randomized treatment period was also dispensed and patients were instructed to start the study drug medication the

next day. During the double-blind treatment period, patients returned for routine safety assessments on Days 23, 27, and 30. This evaluation included vital signs, clinical laboratory testing, recording of concomitant medications and adverse events (AEs), and evaluation of patient compliance with study drug administration. At the final visit of the randomized treatment period, final study assessments and a 12-hour PK study were performed. Vital sign measurements, physical and neurological examinations, and an ECG were performed. Patients completed the SF-MPQ, SF-36, and POMS assessments. Any remaining patient diary data were transmitted, concomitant medications (including use of analgesic agents) and AEs were recorded, and clinical laboratory testing was performed. At the end of the visit, both the Investigator and patient completed the Clinical Global Impression (CGI) of Change survey. Blood samples for the determination of plasma gabapentin levels were obtained on Days 8, 23, 27 and 30. After 60 patients completed the study, an independent Data Safety Monitoring Board (DSMB) reviewed the efficacy and safety data, as defined in the protocol and the board's charter.
Number of Patients (planned and analyzed): The protocol estimated 160 patients would need to be enrolled in the Neurontin treatment period to have 120 patients complete the randomized treatment period of the study (60 per treatment group). The actual patient enrollment was 115 patients into the Neurontin treatment period, with 101 receiving at least 1 dose of the randomized study drug; 47 receiving XP13512 and 54 receiving placebo.
Diagnosis and main criteria for inclusion: Patients 18 through 89 years of age; pain present at the site of a herpes zoster skin rash more than 3 months after healing of the rash; an average pain score by patient history of 4 or greater on a 0-10 point pain scale over the week prior to screening; and an average pain score of 4 or greater on a 0-10 point pain scale over the 1-week baseline period.
Test product, dose and mode of administration, batch number: Orally administered XP13512 sustained release (SR) tablets (manufacturing lot number 04-0224; packaging log number 04-0251). XP13512 is a prodrug of gabapentin. The XP13512 dose was 1200 mg every 12 hours. Note: 1200 mg of XP13512 releases 625 mg of gabapentin.
Duration of treatment: The duration of treatment with open-label Neurontin® was 11 days. The duration of randomized, double-blind study drug treatment (XP13512 or placebo) was 14 days.
Reference therapy, dose and mode of administration, batch number: Orally administered XP13512-matching placebo tablets (manufacturing lot number 04-0223; packaging lot number 04-0250). The placebo-dosing schedule was the same as the XP13512 dosing schedule. An open-label Neurontin treatment period was conducted prior to the randomized double-blind treatment period. The Neurontin® (300 mg tablets, lot numbers 21233v, 01794v, and 014404v) dose was initiated at 300 mg three times daily (TID) and increased over a period of 4 days to a final dose of 600 mg TID, which was maintained for an additional 7 days.
Criteria for evaluation: Efficacy: Primary efficacy variable: change in mean weekly pain scores from baseline assessment to the final study week. Secondary efficacy variables: change from baseline in mean weekly pain scores for each of the two study weeks; change in mean weekly morning pain scores from baseline to the final study week; change in mean weekly evening pain scores from baseline to the final study week; response to treatment, where a responder was as a patient with either a ≥ 30% or ≥ 50% reduction in the mean pain score between baseline and the end of treatment; change in mean weekly morning sleep interference score from baseline to the final study week; change in the five sub-scores of the SF-MPQ from baseline to the final study week; change in the domain scores of SF-36 from baseline to the final study week; change in the domain scores of the POMS from baseline to the final study week; patient CGI of Change

at the end of treatment; Investigator CGI of Change at the end of treatment.

An ad hoc exploratory evaluation was performed on the difference between the end of Neurontin and XP13512 treatment periods to assess the mean weekly pain score, mean morning and evening pain scores, mean weekly morning sleep interference score, SF-MPQ VAS pain score, and SF-MPQ total score. This exploratory analysis defined two subgroups based on the PK analysis as: Group I (> 30% increase in gabapentin plasma levels) and Group II (within 15% of no change in gabapentin plasma levels.)

Safety: Adverse events, clinical laboratory test values (hematology, blood chemistry, and urinalysis), vital signs, and ECG results.

Pharmacokinetics: Gabapentin plasma PK profiles were analyzed at the end of the Neurontin treatment period and at the end of XP13512 treatment. Urine was collected on both PK profile days to measure bioavailability. In addition, on selected days, plasma gabapentin levels were measured.

Statistical methods: Safety analyses were performed using the Safety population that included all patients who were randomized and received at least 1 dose of study drug. Efficacy analyses were performed using the intent-to-treat (ITT) population that included all patients in the Safety population who had at least one mean daily pain score following the start of randomized study medication.

Demographic, baseline data, and patient disposition data were summarized for the two treatment groups using descriptive statistics. Safety and PK data were summarized using descriptive statistics. Comparability was assessed between the two treatment groups using a Pearson chi-square test for gender, race, and ethnicity; and using a two-way analysis of variance (ANOVA) with treatment and site as factors for age, weight, height, time since herpes zoster onset, and duration of PHN.

Descriptive statistics were also provided for efficacy variables. For the primary efficacy variable, an analysis of covariance (ANCOVA) was conducted with treatment, pooled study sites, and treatment-by-site interaction as factors and baseline score as a covariate. For secondary efficacy variables, continuous efficacy variables were analyzed the same way as described for the primary efficacy variables. Counts and percentages were presented for responder analysis and for CGI of Change, and Cochran-Mantel-Haenszel tests adjusted for study site were used to test treatment differences. The p-value for general association was presented for responders, and the p-value from row mean score difference was presented for CGI data.

For those patients randomized to XP13512, the within-group change between the XP13512 and Neurontin treatment periods was assessed using a paired t-test, Fisher's sign test, and McNemar's test (planned analysis and ad hoc analysis).

RESULTS

A total of 115 patients entered into the Neurontin treatment period. A total of 101 patients received at least 1 dose of randomized treatment: XP13512 (n = 47) or placebo (n = 54). Overall, the patients were 23.0 to 87.2 years of age (mean age, 65.0 and 64.0 years in the XP13512 and placebo groups, respectively); 97.9% and 92.6% in the XP13512 and placebo groups, respectively, were Caucasian; and approximately half in each treatment group were female. The mean duration of PHN was 3.7 years in the XP13512 group and 2.7 years in the placebo group. The mean time since herpes zoster onset was 3.7 years in the XP13512 group and 2.9 years in the placebo group.

EFFICACY RESULTS: As shown in the following table, at the final week of treatment (Week 2 or the last 7 days of treatment for those [n = 9] patients who did not complete 14 days), the mean decrease from baseline in mean weekly pain scores was significantly greater (indicating greater improvement) for XP13512 compared with placebo.

	Placebo (N = 54)	XP13512 (N = 47)	p-value [1]
Baseline, mean ± SD [2]	6.1 ± 1.23	6.2 ± 1.22	0.7443
Change from baseline, mean ± SD [2]	-1.2 ± 1.69	-2.1 ± 1.63	0.0321
30% Improvement, n (%)	15 (27.8)	26 (55.3)	0.0073
50% Improvement, n (%)	10 (18.5)	13 (27.7)	0.2582

ANCOVA = analysis of covariance; ANOVA = analysis of variance; SD = standard deviation

[1] P-value for the baseline observations is for treatment effect from two-way ANOVA. P-value for post-baseline treatment effect is from two-way ANCOVA with baseline score as a covariate for continuous responses, and from Cochran-Mantel-Haenszel test stratified by study center for categorical responses.

[2] The pain scale was from 0 to 10 and higher scores indicate more severe pain. A negative change from baseline indicates a reduction in pain.

After the first week, the mean decrease (improvement) from baseline in mean weekly pain scores was greater with XP13512, meeting statistical significance (p = 0.0229) compared with treatment with placebo. Mean changes in weekly pain scores were -1.7 in the XP13512 treatment group and -1.0 in the placebo treatment group at the end of Week 1. After the second (final) week, the mean decrease (improvement) from baseline in mean weekly pain scores was significantly greater (p = 0.0269) for XP13512 compared with placebo treatment; mean changes from baseline in mean weekly pain scores were -2.1 in the XP13512 treatment group and -1.2 in the placebo group.

After the final week, the mean decrease (improvement) from baseline in mean weekly morning pain score was greater, meeting statistical significance, with XP13512 compared with placebo treatment (-2.3 versus -1.1, p = 0.0084). In contrast, mean decreases from baseline in mean weekly evening pain score did not reach a statistically significant difference between XP13512 and placebo treatment (-1.9 versus -1.2, p = 0.1829).

There was a statistically significant difference between the treatment groups in the percentages of patients who showed at least a 30% improvement in mean weekly pain scores at the end of the 2-week treatment period (55.3% of patients in the XP13512 treatment group versus 27.8% of patients in the placebo group, p = 0.0073); and mean weekly morning pain scores (61.7% versus 27.8%, p = 0.0009).

After the final week of treatment, the mean decrease from baseline in mean weekly morning sleep interference score was statistically significantly greater (indicating less sleep interference) for patients treated with XP13512 compared with placebo (-2.2 versus -0.9, p = 0.0010).

For the SF-MPQ, statistically significantly greater improvements were noted in the XP13512 treatment group versus the placebo group in total score, sensory score, visual analogue scale (VAS) score, and present pain intensity score. For the SF-36, statistically significantly greater improvements were noted in the XP13512 treatment group versus the placebo group in the role-physical domain, bodily pain domain, vitality domain, and mental health domain. For the POMS, statistically significantly greater improvements were noted in the XP13512 treatment group versus the placebo group in the total mood disturbance domain, depression-dejection domain, anger-hostility domain, and vigor-activity domain.

For the patient's CGI of Change, 42.6% of patients in the XP13512 treatment group rated themselves "very much improved" or "much improved" compared with 13.5% of patients in the placebo group; across all categories, the difference was statistically significant (p = 0.0003). For the Investigator's CGI of Change, 40.4% of patients in the XP13512 treatment group were very much improved or much improved compared with 9.4% of patients in the placebo group; across all categories, the difference was statistically significant (p = 0.0003).

In the subgroup analysis comparing the Neurontin and XP13512 treatment periods for those patients

treated with XP13512, statistically significant improvements comparing the end of the Neurontin treatment period to the end of the XP13512 treatment period were noted in mean weekly pain scores ($p = 0.0454$), mean weekly morning pain scores ($p = 0.0392$), and the percentages of patients with at least a 30% improvement relative to baseline for mean weekly morning pain scores ($p = 0.0209$), mean weekly morning sleep interference score ($p = 0.0067$), and the SF-MPQ VAS pain score ($p = 0.0455$) favoring XP13512. Compared to Neurontin®, the improvement in mean weekly pain score was statistically significant for patients in Group I who had a > 30% increase in gabapentin plasma levels (-0.9; $p = 0.0126$), but was not statistically significant in Group II who were within 15% of no change in gabapentin plasma levels (-0.2; $p = 0.4841$).

SAFETY RESULTS: For the 115 patients who received Neurontin® during the Neurontin treatment period, the most frequent (≥ 5%) reported AE was dizziness (13.9%). During the randomized treatment period, at least one treatment emergent adverse event (TEAE) was reported for 25 patients (46.3%) in the placebo treatment group and for 25 patients (53.2%) of patients in the XP13512 treatment group. The most frequent (≥ 5%) TEAEs that occurred in patients in the XP13512 treatment group were dizziness (21.3%), headache (8.5%), nausea (8.5%), and diarrhea (6.4%). TEAEs that occurred in at least 5% of the placebo group were nausea (9.3%); headache, insomnia, and fatigue (7.4% for each); and dizziness, PHN, and depression (5.6% for each). Most patients with TEAEs had events that were of mild or moderate severity; 5 patients had severe TEAEs (1 patient [2.1%] in the XP13512 treatment group and 4 [7.4%] in the placebo group). Treatment-related TEAEs were reported for 31.5% of patients in the placebo group and for 40.4% of patients in the XP13512 treatment group.

There were no deaths and no treatment-emergent serious adverse events (SAEs). One patient had an SAE (pancreatitis) during the screening period, prior to study drug treatment. Four patients were discontinued due to AEs in during the Neurontin treatment period (dizziness [2 patients], tachycardia [1 patient], and lethargy [1 patient]). Four patients, all in the placebo group, were discontinued from the study due to AEs (increased PHN-related pain [2 patients], dizziness [1 patient], and non-cardiac chest pain [1 patient]).

Treatment with either XP13512 or placebo had no clinically meaningful effects on clinical laboratory test results, vital signs, or ECG findings, which is consistent with the known safety profile of gabapentin.

PHARMACOKINETICS RESULTS: The study was designed to provide insight into the comparative PK of XP13512 tablets and the currently approved regimen of Neurontin® (600 mg TID). Blood samples were collected from patients prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing at Visit 3 (Day 19); samples were collected prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after dosing at Visit 7 (Day 33). Plasma data for PK analysis were available from a total of 98 patients (47 males and 51 females). Complete urine output was obtained over 0-8 hr on Visit 3 and 0-12 hr on Visit 7 and data available from a total of 86 patients.

Exposure to gabapentin in plasma after oral dosing of Neurontin® was variable among patients. For the 98 patients with plasma data on Neurontin®, concentrations of gabapentin in plasma reached a mean ± standard deviation (SD) steady state maximum concentration (Css, max) of 8.63 ± 2.60 μg/mL at a time to Css, max (Tmax) of 2.52 ± 1.25 hr post-dosing. The steady state 24-hour area under the concentration curve (AUC(0-24)) was 160 ± 48.4 μg*hr/mL and the average plasma concentration at steady state (Css, ave) was 6.68 ± 2.02 μg/mL. The mean oral bioavailability of gabapentin in these patients was 45.1 ± 20.1% (n = 86), based on urinary recovery.

Pharmacokinetic data were available for a total of 42 patients who received both Neurontin® and XP13512. Of these, 42 had available plasma data and 38 had available urine data for both treatments. In these patients, following oral dosing of Neurontin®, concentrations of gabapentin reached a mean ± SD Css, max of 9.07 ± 3.00 μg/mL (n = 42) at a Tmax of 2.31 ± 1.13 hr post-dosing. The steady state AUC(0-24) was 166 ± 54.1 μg*hr/mL and the Css, ave was 6.93 ± 2.25 μg/mL. The mean oral bioavailability of gabapentin in these patients was 43.3 ± 19.8% (n = 38), based on urinary recovery.

Following oral administration of XP13512 in the same patients, concentrations of gabapentin reached a mean Css, max of 11.0 ± 3.99 µg/mL (n = 42) at a Tmax of 4.63 ± 2.45 hr post-dosing. The steady state AUC(0-24) was 194 ± 69.9 µg*hr/mL and the Css, ave was 8.10 ± 2.91 µg/mL. The mean oral bioavailability of gabapentin in these patients was 76.8 ± 26.4% (n = 38), based on urinary recovery.

The regimen of XP13512 used in this study (1200 mg BID or 1250 mg-equivalents of gabapentin per day) represents a 31% lower dose of gabapentin equivalents compared to the Neurontin® regimen (600 mg TID or 1800 mg-equivalents of gabapentin per day). Despite the lower total dose of gabapentin, XP13512 tablets provided, on average, a 17% increase in the average steady state gabapentin plasma concentration relative to that produced by Neurontin® in the same patients ($p = 0.0050$; paired t-test).

Oral bioavailability of gabapentin from XP13512 tablets was 77% greater than from Neurontin® capsules ($p < 0.0001$; paired t-test). Inter-patient variability in absorption was lower for XP13512 (CV = 33%) than for Neurontin® (CV = 46%). Fifteen patients (36%) had increased average gabapentin plasma concentrations of greater than 30% during XP13512 treatment compared to Neurontin® treatment (Group I), while 13 patients were within 15% of no change in average gabapentin plasma concentrations (Group II).

CONCLUSIONS: Overall, XP13512 provided statistically significant and clinically relevant benefits to patients with PHN when administered twice a day.

Compared with placebo, treatment with XP13512 resulted in statistically significant and clinically meaningful improvements from baseline in:

- Mean weekly pain scores at the end of treatment (the primary efficacy variable) and for Week 1 and Week 2 of treatment.
- Mean weekly morning pain scores.
- Mean weekly morning sleep interference score.
- Ratings by the patient and Investigator of CGI of Change.

The SF-MPQ for four of the five subscores (total score, sensory score, VAS pain score, and present pain intensity score), in the SF-36 for four of the eight domains (role-physical, bodily pain, vitality, and mental health), and in the POMS for four of the seven domains (total mood disturbance, depression-dejection, anger-hostility, and vigor-activity).

In addition, treatment with XP13512 resulted in statistically significant improvements over the Neurontin treatment period in mean weekly pain scores, mean weekly morning and evening pain scores, mean weekly morning sleep interference score, and 2 of 5 SF-MPQ subscales. A statistically significant within-group improvement from the end of the Neurontin treatment period to the end of XP13512 treatment was seen in mean weekly pain scores and mean weekly morning pain scores, percentage of patients with at least 30% improvement in mean weekly morning sleep scores, and percentage of patients with at least 50% improvement in the SF-MPQ VAS.

Treatment with XP13512 resulted in a higher incidence of dizziness compared with treatment with placebo. Dizziness was also reported during treatment with Neurontin® (13.9%), but at a lower rate than with XP13512 (21.3%). This may be related to the higher drug levels of gabapentin produced by XP13512 compared with Neurontin®. However, dizziness did not result in the withdrawal of any XP13512-treated patients. Treatment with XP13512 had no clinically meaningful effects on clinical laboratory tests (including hepatic and renal function tests), vital signs, or ECG findings, which is consistent with the known safety profile of gabapentin.

Date of report: 21 June 2006

4.3 Pharmacometric Review by Dr. Li Zhang

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

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

1.1.1 Is the proposed dosing regimen for HORIZANT (gabapentin enacarbil, GEn) in Postherpetic Neuralgia Patients with varying degrees of renal function acceptable?

The proposed dosing regimen (Table 1) for HORIZANT in Postherpetic Neuralgia patients with varying degrees of renal function is acceptable. However, the proposed dosing guidelines for End-Stage Renal Disease (ESRD) groups of renal impaired patients are not acceptable.

Table 1. Adjustment of Dosage of HORIZANT for Patients with Postherpetic Neuralgia in Accordance With Creatinine Clearance

Creatinine Clearance (mL/min)	Titration	Maintenance	Tapering
≥60	600 mg in AM for 3 days	600 mg twice daily	600 mg in AM for 1 week
30 - 59	300 mg in AM for 3 days	300 mg twice daily. Increase to 600 mg twice daily as needed[a]	Reduce current maintenance dose to once daily in AM for 1 week
15 - 29	300 mg in AM on Day 1 and Day 3	300 mg in AM. Increase to 300 mg twice daily if needed[a]	If taking 300 mg twice daily, reduce to 300 mg once daily in AM for 1 week. If taking 300 mg once daily, no taper needed.
<15	None	300 mg every other day in AM. Increase to 300 mg once daily in AM if needed[a]	None
~~<15 on hemodialysis~~	~~None~~	~~300 mg following every dialysis. Increase to 600 mg following every dialysis if needed[a]~~	~~None~~
[redacted]			

(b) (4)

[a] Based on tolerability and efficacy

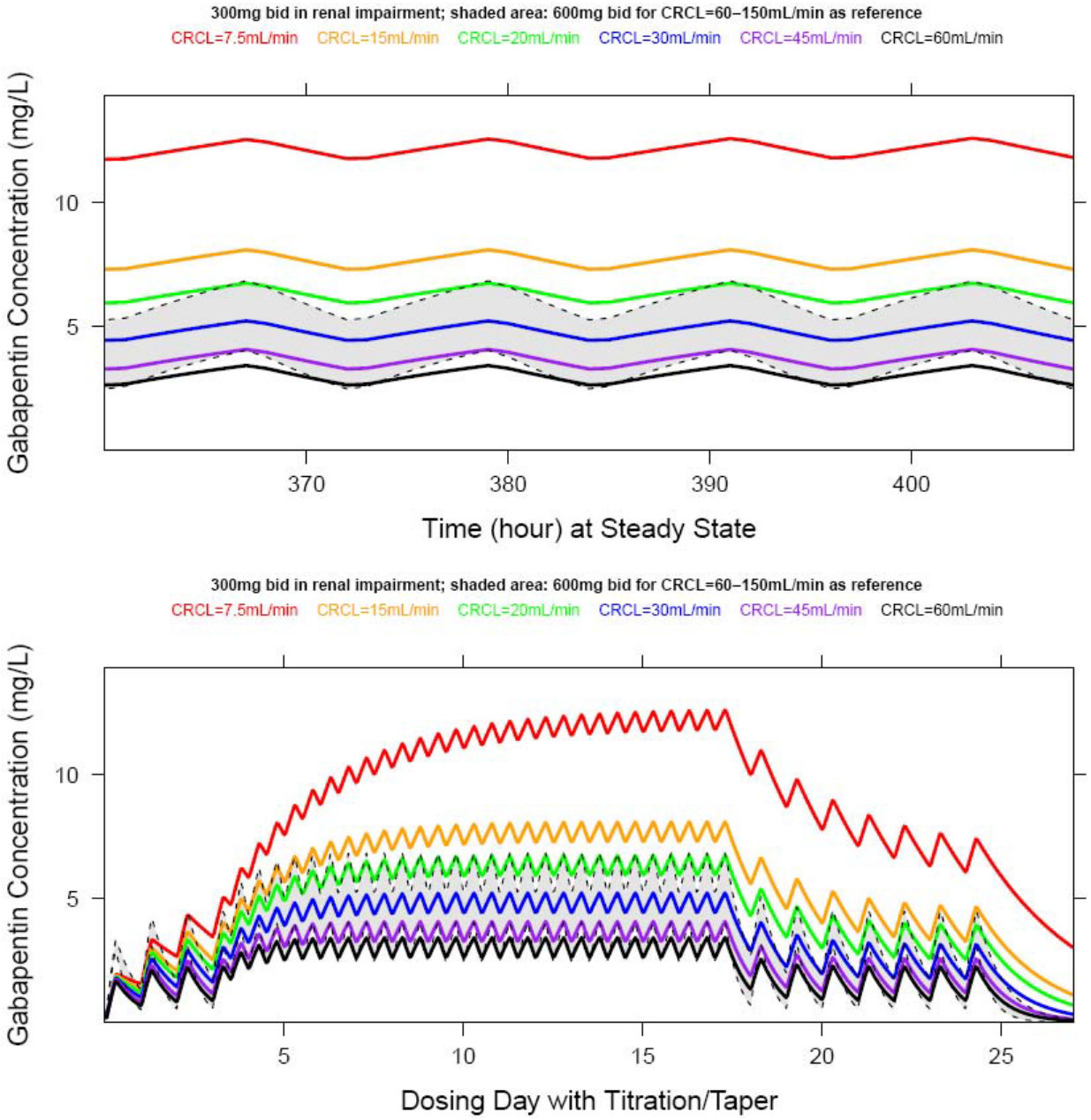
In pivotal trial PXN110748, normal patients were randomized to receive either oral HORIZANT 3600 mg/day, 2400 /day, 1200 mg/day, or matching placebo. Following absorption, gabapentin is eliminated exclusively by renal excretion. HORIZANT apparent clearance was lower in subjects with reduced creatinine clearance. Dose adjustment is required in subjects with renal impairment. FDA review for Restless legs syndrome (RLS) application has described CL/F of gabapentin is approximately proportional to creatinine clearance (CRCL).

The range of CRCL among PHN patients who were enrolled in the pivotal trial PXN110748 was 60-150mL/min, which was considered as the reference range for normal renal function for the simulations. For patients with CRCL < 60mL, simulations were conducted to identify dose regimens that would generate similar exposure as the reference range. The simulated dose regimens have been selected with the assumption that HORIZANT is available as oral tablets of 600mg and 300mg.

1.1.1.1 Renal Impairment Other than ESRD

Time course of gabapentin plasma concentrations was simulated for non-ESRD patients with a range of CRCL values between 7.5mL/min and 60mL/min, at the maintenance dose of 300mg b.i.d., 300mg q.d. and 300mg q.o.d. Consistent with the proposed dose recommendation for patients with normal renal function, a titration phase and a taper phase, both of which employed a dosing rate that is half of that at the maintenance phase, was included in the simulation where judged appropriate. The results are shown in Figure 1, Figure 2 and Figure 3, where the upper panels represent the maintenance phase only; and the lower panels illustrate entire treatment duration including titration, maintenance and taper phases where applicable.

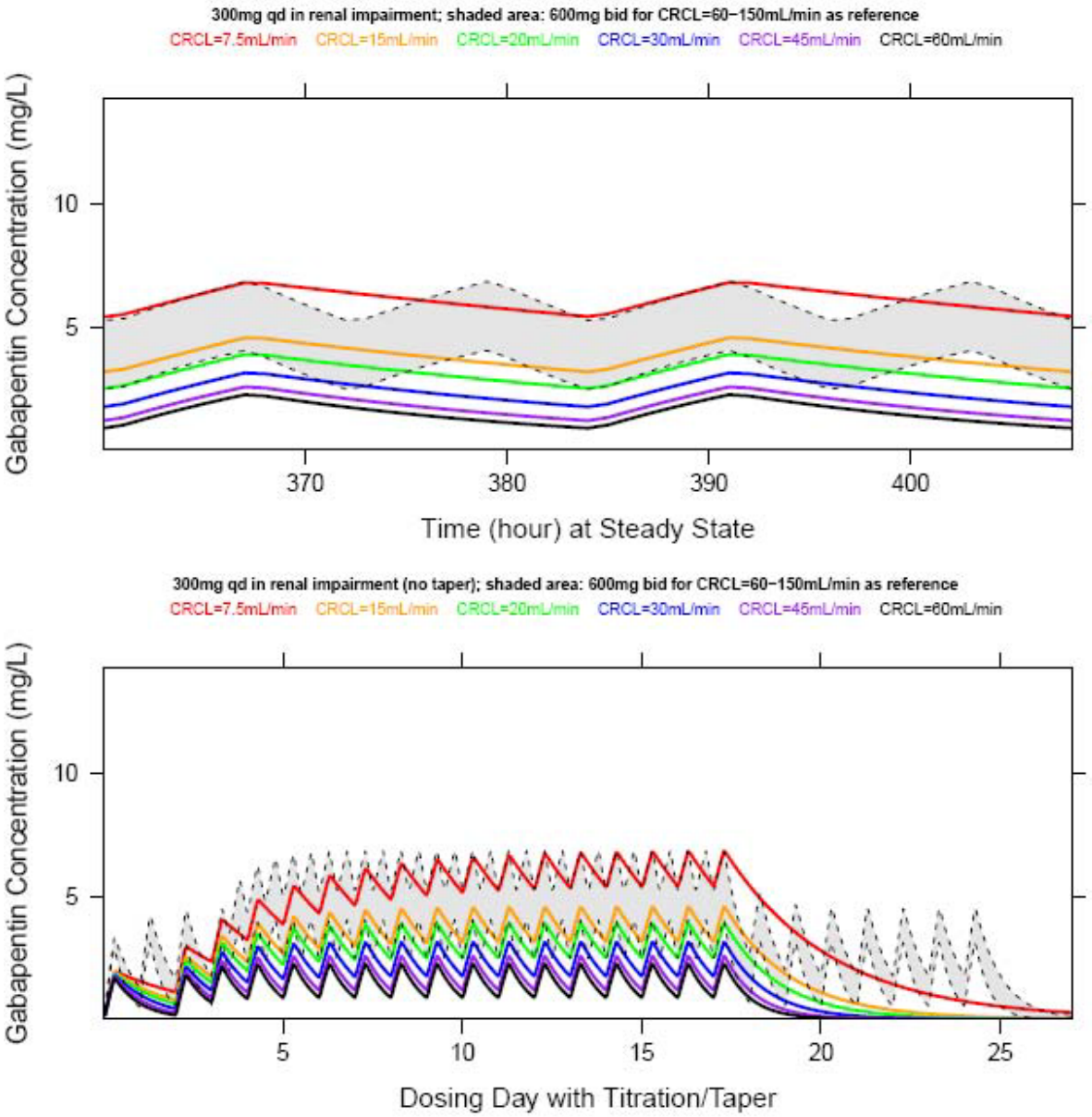
Figure 1. Simulated Plasma Concentration of Gabapentin in Renal Impairment at Maintenance Dose of HORIZANT 300mg b.i.d.



Source: Figure 5 on page 27, from Summary-Clinical-Pharm-PHN

The simulations show that 300mg b.i.d. would allow subjects with CRCL 20 - 60mL/min to achieve concentrations comparable to the reference range, and the concentrations in subjects with CRCL 30- 59 mL/min to be consistently at the lower end of the reference range. Therefore sponsor's proposed for patients with CRCL 30- 59 mL/min "*300 mg twice daily. Increase to 600 mg twice daily as needed*" is acceptable.

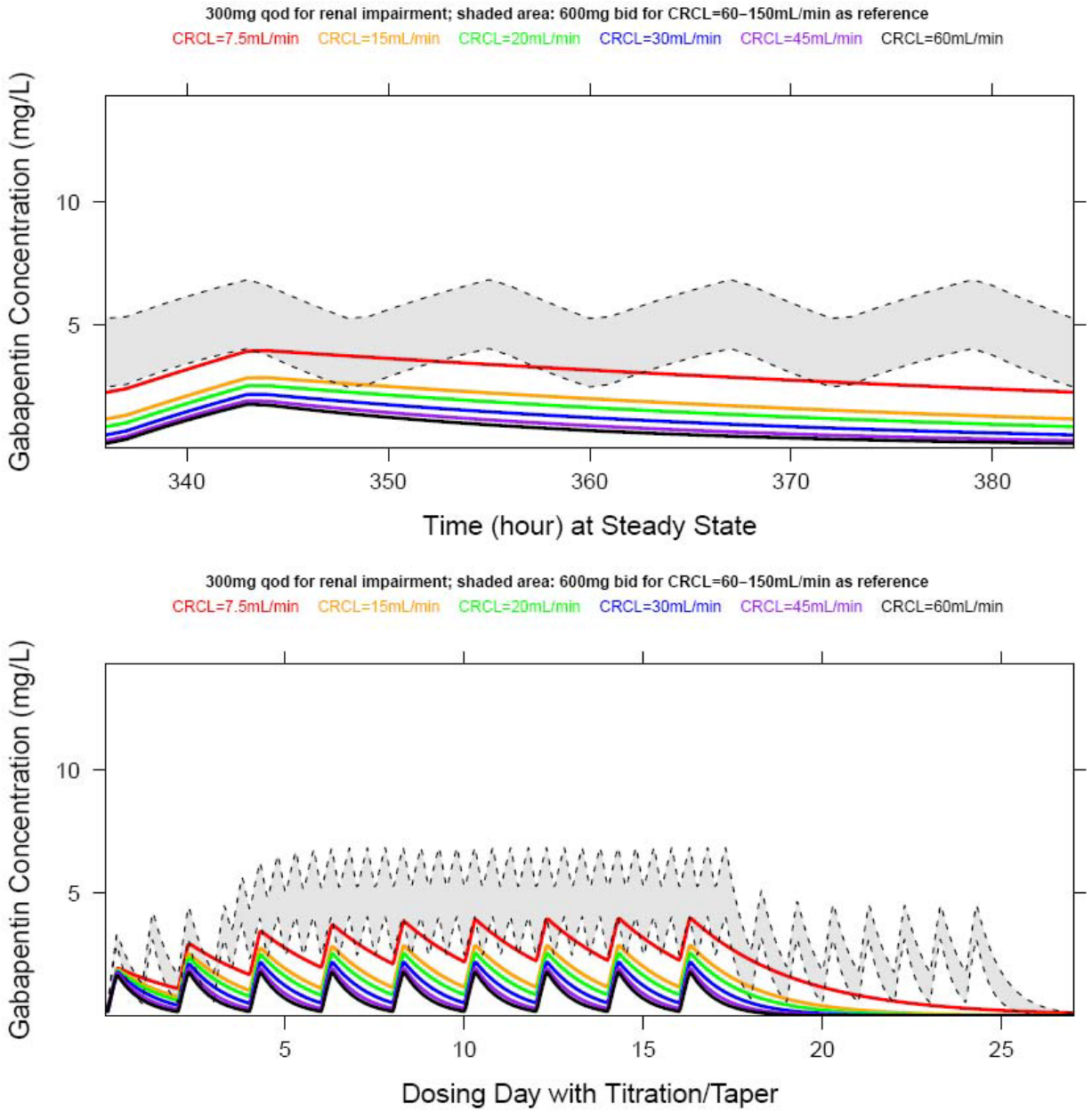
Figure 2. Simulated Plasma Concentration of Gabapentin in Renal Impairment at Maintenance Dose of HORIZANT 300mg q.d.



Source: Figure 6 on page 28, from Summary-Clinical-Pharm-PHN

The simulations show that 300mg q.d. appears to allow subjects with CRCL 7.5 - 30mL/min to achieve concentrations comparable to the reference range, and the concentrations in subjects with CRCL 15- 30mL/min to be consistently lower than the reference range. Therefore sponsor's proposed for patients with CRCL 15- 29 mL/min "*300 mg in AM. Increase to 300 mg twice daily if needed*" is acceptable.

Figure 3. Simulated Plasma Concentration of Gabapentin in Renal Impairment at Maintenance Dose of HORIZANT 300mg q.o.d.



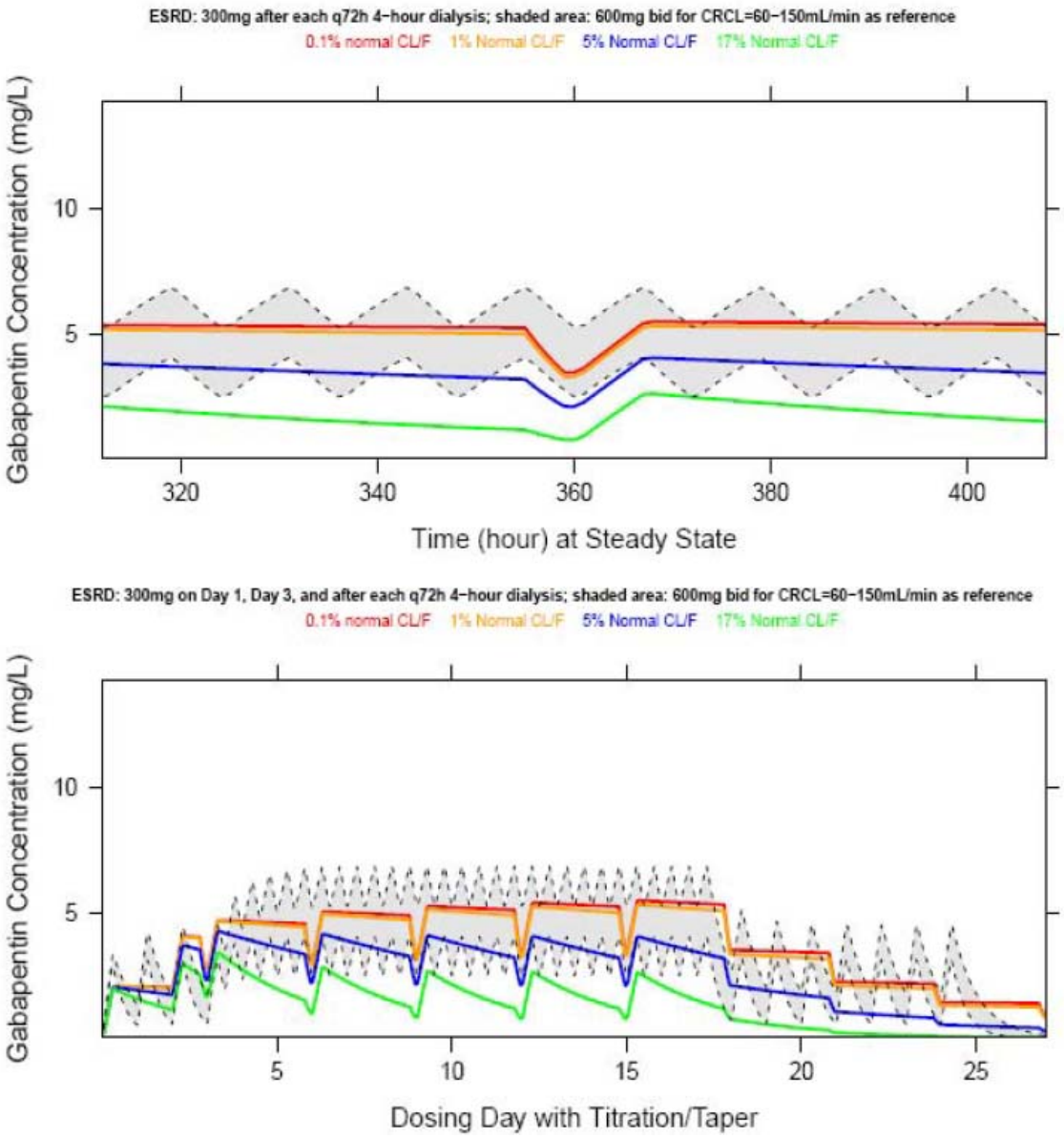
Source: Figure 7 on page 29, from Summary-Clinical-Pharm-PHN

The simulations show that 300mg q.o.d. appears to allow subjects with CRCL 7.5 – 15 mL/min to achieve concentrations comparable to the reference range, and the concentrations in subjects with CRCL <15mL/min to be consistently lower than the reference range. Therefore sponsor's proposed for patients with CRCL <15 mL/min "*300 mg every other day in AM. Increase to 300 mg once daily in AM if needed*" is acceptable.

1.1.1.2 End-Stage Renal Disease

The population PK model did not have an ESRD (End-Stage Renal Disease) component. Sponsor assumed CRCL values of 0.056, 0.11, 1.2 and 7.5mL/min in the model, covering the range from complete lack of renal function to borderline ESRD. According to the model, those values corresponded to 0.1, 1, 5 and 17% of the 6.25L/h CL/F at CRCL of 104mL/min, the median value for the model dataset. For the simulations, 4-hour haemodialysis sessions were assumed to occur every 72hours, with the dialysis clearance of 132mL/min that was estimated in study XP066. The simulated dose regimen was 300mg initial dose, 300mg on day three, and 300mg at the completion of each dialysis. The results are shown in Figure 4.

Figure 4. Simulated Plasma Concentration of Gabapentin in ESRD Patients at Maintenance Dose of HORIZANT 300 mg following every dialysis



Source: Figure 8 on page 31, from Summary-Clinical-Pharm-PHN

Reviewer's Comment:

The simulations show that adequate exposure can be achieved for patients with up to 5% of normal CL/F. While for redosing after dialysis, Dr. Veneeta Tandon and Dr. Atul Bhattaram's clinical pharmacology review for the original NDA on 6/24/2011 discussed that although the mean exposure values such as $AUC_{SS,24}$ and $C_{SS,max}$ for gabapentin in these ESRD subjects given HORIZANT after every other dialysis were similar to mean values in normal subjects, the flat profile (two day profile) of exposure in patients on

dialysis inevitably departs from the profile in subjects with normal renal function. Given the fact that ESRD subjects will have varying dialysis times, and potentially varying HORIZANT dosing schedules, there is no dosing and dialysis scenario that is practically possible that would provide a profile in all ESRD subjects that never exceeds the exposures in normal subjects. To be consistent with clinical pharmacology review for RLS patients, HORIZANT dosing is therefore not recommended in subjects with ESRD and on dialysis for PHN patients.

1.2 Recommendations

The labeling changes on page 3 of this review have been conveyed to the sponsor. Reviewer changes are shown in yellow highlight. The sponsor's changes are shown by track changes.

2 PERTINENT REGULATORY BACKGROUND

HORIZANT is a pro-drug of garbapentin that is converted to garbapentin upon absorption from the GI tract. HORIZANT was investigated under IND 068341 (as XP13512) for the treatment of patients with postherpetic neuralgia (PHN) and neuropathic pain associated with DPN ((b) (4) for migraine headache prophylaxis under the XenoPort-sponsored IND 101677; and treatment of moderate-to-severe primary restless leg syndrome (RLS) under IND 071352. The GEn RLS clinical development program consisted 17 Phase I studies, a population PK/PD analysis, and 8 Phase 2/3 studies. The RLS NDA was approved on 06 April 2011.

On 09 August 2011, GSK submitted a supplemental NDA 22399 for HORIZANT for the indication of the management of PHN in adults. This sNDA is submitted under Section 505(b)(2) pathway as it relies on information regarding HORIZANT that GSK does not own or to which GSK does not have a right of reference, including the Agency's findings of safety and effectiveness for Neurontin (HORIZANT) (NDA 20235). The approved 600 mg HORIZANT tablet was used in all clinical efficacy/safety studies that support the current sNDA.

The overall PHN clinical development program consisted the 17 Phase I (previously submitted to the RLS NDA and were reviewed by the clinical pharmacology review team supporting DNP) and 3 Phase II PHN studies (pivotal study PXN110748 (included in this sNDA), and supportive studies (PXN110527 (included in this sNDA) and XP009 (submitted in the original NDA)).

Study PXN110748: An efficacy and safety study of HORIZANT compared with a concurrent placebo control in subjects with neuropathic pain associated with post-herpetic neuralgia.

Study PXN110527: the investigation of the efficacy and pharmacokinetics of HORIZANT in subjects with neuropathic pain associated with post-herpetic neuralgia who have had an inadequate response to HORIZANT treatment.

Study XP009: A multi-center, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of XP13512 in patients with postherpetic neuralgia.

3 DATA SETS USED ARE SUMMARIZED IN TABLE 2.

Table 2. Analysis Data Sets

Study Number	Name	Link to EDR
PXN110748	pkeff_PXN110748.xpt	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gabapentin__NDA22399_LZ\sNDA 022399 S003 (HORIZANT_GSK)\Data
PXN110748	pknm_PXN110748.xpt	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gabapentin_NDA22399_LZ\sNDA 022399 S003 (HORIZANT_GSK)\Data

4 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Efficacy.ssc	Dose-response	Reviews\Ongoing PM Reviews Gabapentin__NDA22399_LZ\sNDA 022399 S003 (HORIZANT_GSK)\Data\Processed
1.WMF	Figure 2	Reviews\Ongoing PM Reviews\ Gabapentin__NDA22399_LZ\sNDA 022399 S003 (HORIZANT_GSK)\Data\Processed

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

/s/

WEI QIU
05/03/2012

LI ZHANG
05/03/2012

VENKATESH A BHATTARAM
05/03/2012

YUN XU
05/03/2012

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-399 S3**	**Brand Name**	**Horizant™ ER tablets**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Gabapentin enacarbil**
Medical Division	**DARRP**	**Drug Class**	
OCP Reviewer	**Wei Qiu, Ph.D.**	**Indication(s)**	**Management of Postherpetic Neuralgia (PHN) in adults**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**Tablets; 300 and 600 mg**
Pharmacometrics Reviewer		**Dosing Regimen**	**600 mg in the morning for 3 days, increased to 600 mg BID (1200 mg/day) on day 4**
Date of Submission	**August 9, 2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**April 2, 2012**	**Sponsor**	**GSK**
Medical Division Due Date	**April 9, 2012**	**Priority Classification**	**standard**
PDUFA Due Date	**June 9, 2012**	**Relevant INDs**	**IND 68,341**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**x**	**1**		**XP009 (submitted in the original NDA)**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:	**x**			**See above**
Phase 3:				
PK/PD -				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Phase 1 and/or 2, proof of concept:	**x**	**2**		**Studies 110527 & PXN110748**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**x**			**See above**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√	All Phase 2/3 studies used the commercial formulation 600 mg. A Prior Approval Supplement to register 300 mg was submitted on 24 June 2011 (NDA 022399/S-002) and is currently under review.
2	Has the applicant provided metabolism and drug-drug interaction information?			√	The metabolism and DDI data were submitted in the original NDA and reviewed by the clinical pharmacology reviewer supporting DNP.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			√	See above
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?		√		Will ask sponsor to submit the assay validation report and with-in study bioanalytical report for Studies XP009, PXN110748, and 110527.
5	Has a rationale for dose selection been submitted?	√			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	√			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	√			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	√			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	√			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	√			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		√		A waiver of the requirement to conduct a pediatric assessment for this indication was granted by the Agency due to the low incidence in the pediatric population which makes the pediatric studies infeasible.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	See above
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this	√			

	product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

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

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

Submit the assay validation report and within-in study bioanalytical report for Studies XP009, PXN110748, and 110527. If you have submitted these reports, please help us to locate them.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Background:

Gabapentin enacarbil (GEn) is a pro-drug of gabapentin that is converted to gabapentin upon absorption from the GI tract. GEn was investigated under IND 068341 (as XP13512) for the treatment of patients with postherpetic neuralgia (PHN) and neuropathic pain associated with DPN (b) (4); for migraine headache prophylaxis under the XenoPort-sponsored IND 101677; and treatment of moderate-to-severe primary restless leg syndrome (RLS) under IND 071352. The GEn RLS clinical development program consisted 17 Phase I studies, a population PK/PD analysis, and 8 Phase 2/3 studies. The RLS NDA was approved on 06 April 2011.

As part of PMR, sponsor was required to conduct the following studies: (1) an in vitro study to evaluate the potential for gabapentin enacarbil and gabapentin to be inhibitors of CYP2C8 and CYP2B6; (2) an in vitro dissolution study to evaluate alcohol dose dumping using the final dissolution method, and evaluate different concentrations of alcohol up to 40% (0, 5, 10, 20, and 40%); (3) an adequate, randomized, double-blind, placebo- and moxifloxacin-controlled trial to evaluate the effect of gabapentin enacarbil on cardiac repolarization in healthy adult subjects; (4) a clinical drug-drug interaction trial to evaluate the pharmacokinetic and the pharmacodynamic interaction between gabapentin enacarbil and morphine. In PMC, sponsor is asked to develop a dosage form that will allow for a 300 mg dose that could be taken once daily in patients with severe renal impairment, including patients on hemodialysis.

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Following approval of the RLS NDA on 06 April 2011, sponsor submitted study protocol 11DMW017 to evaluate the in vitro inhibition of 2B6 and 2C8 by gabapentin and GSK1838262 on May 25, 2011. On 09 June 2011, sponsor submitted in vitro alcohol dose dumping study and simulation of in vivo impact of alcohol. Sponsor developed 300 mg strength and requested biowaiver and submitted PK simulation to support dose adjustment in patients with impaired renal function on 24 June 2011 and it is currently under review by DNP. The study protocols RXP115720 for DDI with morphine and RXP114112 thorough QT study protocol were submitted on July 28, 2011 and August 29, 2011, respectively.

On 09 August 2011, GSK submitted a supplemental NDA 22399 for Horizant for the indication of the management of PHN in adults. This sNDA is submitted under Section 505(b)(2) pathway as it relies on information regarding gabapentin that GSK does not own or to which GSK does not have a right of reference, including the Agency's findings of safety and effectiveness for Neurontin (gabapentin) (NDA 20235). The approved 600 mg GEn ER tablet was used in all clinical efficacy/safety studies that support the current sNDA.

The overall PHN clinical development program consisted the 17 Phase I (previously submitted to the RLS NDA and were reviewed by the clinical pharmacology review team supporting DNP) and 3 Phase II PHN studies (pivotal study PXN110748 (included in this sNDA), and supportive studies (PXN110527 (included in this sNDA) and XP009 (submitted in the original NDA)).

Study PXN110748: An efficacy and safety study of gabapentin enacarbil compared with a concurrent placebo control in subjects with neuropathic pain associated with post-herpetic neuralgia.
Study PXN110527: the investigation of the efficacy and pharmacokinetics of gabapentin enacarbil in subjects with neuropathic pain associated with post-herpetic neuralgia who have had an inadequate response to gabapentin treatment.
Study XP009: A multi-center, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of XP13512 in patients with postherpetic neuralgia.

In order to provide PK bridging between GEn and the RLD Neurontin tablets (NDA 20235), sponsor compared the systemic exposure for the proposed therapeutic dose of GEn 1200 mg/day (either observed or predicted in XP009, PXN110527, PXN110748, XP084) to the maximum therapeutic dose of Neurontin 1800 mg/day (observed in Study XP009) and the starting dose of Neurontin 900 mg/day (reported in literature).

Sponsor's summary on comparison of gabapentin exposure for Horizant and Neurontin and pro-drug exposure:

- *Comparison of gabapentin exposure for Horizant and Neurontin*: Neurontin label states "In adults with postherpetic neuralgia, Neurontin therapy may be initiated as a single 300 mg dose on Day 1, 600 mg/day on Day 2 (divided BID), and 900 mg/day on Day 3 (divided TID). The dose can be subsequently be titrated up as needed for pain relief to a daily dose of 1800 mg (divided TID)." Sponsor concluded that the mean average steady state concentrations of gabapentin at 1200 mg/day of GEn were consistently predicted to be approximately 40% lower than those at 1800 mg/day Neurontin. Further, the

- *Pro-drug exposure*: Sponsor concluded that in a series of 8 clinical studies, the relative systemic exposure to intact GEn after oral dosing of GEn was consistently less than 0.5% of the corresponding systemic exposure to gabapentin in terms of AUC, regardless of GEn dose, formulation, or the presence of food. In the approved label, it stated that "Levels of gabapentin enacarbil in blood are low and transient (≤ 2% of corresponding gabepentin plasma levels)".

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/s/

WEI QIU
10/03/2011

YUN XU
10/03/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-399/S-003

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 022399	NDA Supplement #: S- 003	Efficacy Supplement Type SE- 1
Proprietary Name: Horizant Established/Proper Name: gabapentin encarbil Dosage Form: Extended-Release Tablets Strengths: 1200 mg (600 mg BID)		
Applicant: Glaxo Group Ltd		
Date of Receipt: August 9, 2011		
PDUFA Goal Date: June 9, 2012	Action Goal Date (if different): June 6, 2012	
Proposed Indication: Postherpetic Neuralgia		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Neurontin, NDA 20235	Clinical and clinical pharmacology sections of label
Published literature	Nonclinical, clinical and clinical pharmacology sections of label

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Bioavailability studies

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

Neurontin

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Neurontin	20235	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☒ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The application and this supplement provides for a change in dosage form from capsules to tablets. Also, a change in formulation to extended-release as well as change in dosing regimen from 600 mg TID to 600 mg BID.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): NDA 20882, Neurontin Oral Tablet; NDA 21129, Neurontin Oral Solution; NDA 22544 Gralise and also approved generics

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): Neurontin: 6054482
6054482*PED

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 6054482; 6054482*PED

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): August 11, 2011

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

SHARON M TURNER RINEHARDT
06/05/2012

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Anesthesia, Analgesia, and Addiction Products

Application Number: NDA 022399/S-003

Name of Drug: Horizant

Applicant: GlaxoSmithKline

Material Reviewed: Labeling submitted during labeling negotiations

Submission Dates: August 9, 2011
Receipt Date: August 9, 2011

Type of Labeling Reviewed: WORD

Background and Summary

On August 9, 2011, the Division of Anesthesia, Analgesia, and Addiction Products received an efficacy supplement to add the indication, postherpetic neuralgia, to the package insert for NDA 22399 as well as update the medication guide. This is a high level review of the major changes accepted during negotiation of the labeling for NDA 22399/S-003

Review

Please note that an underline indicates an addition to the approved label.

HIGHLIGHTS OF PRESCRIBING INFORMATION: The following significant changes were noted:

---------- RECENT MAJOR CHANGES ------

Indications and Usage, Management of Postherpetic Neuralgia (1.2)	06/2012
Dosage and Administration, Postherpetic Neuralgia (2.2)	06/2012
Dosage and Administration, Renal Impairment (2.3)	06/2012
Warnings and Precautions, Somnolence/Sedation and Dizziness (5.2)	06/2012
Warnings and Precautions, DRESS (5.5)	12/2011
Warnings and Precautions, Discontinuation of HORIZANT (5.6)	06/2012

----------INDICATIONS AND USAGE -------

HORIZANT is indicated for:

- treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults. (1.1)
- management of postherpetic neuralgia (PHN) in adults. (1.2)

-------DOSAGE AND ADMINISTRATION --

Instruct patients to swallow tablets whole and not to cut, crush, or chew tablets. Take with food. (2)

RLS: 600 mg once daily taken at about 5 PM. (2.1)

- A dose of 1,200 mg once daily provided no additional benefit compared with the 600-mg dose, but caused an increase in adverse reactions. (2.1)
- If the dose is not taken at the recommended time, the next dose should be taken the following day as prescribed. (2.1)

PHN: The starting dose is 600 mg in the morning for 3 days, then increase to 600 mg twice daily beginning on day 4. (2.2)

- A daily dose greater than 1,200 mg provided no additional benefit. (2.2)
- If the dose is not taken at the recommended time, skip this dose, and the next dose should be taken at the time of next scheduled dose. (2.2)
- Patients with renal impairment: Doses of HORIZANT must be adjusted in accordance with renal function. (2.3)

--------WARNINGS AND PRECAUTIONS ---

- Driving impairment: Warn patients not to drive until they have gained sufficient experience with HORIZANT to assess whether it will impair their ability to drive. (5.1)
- Somnolence/sedation and dizziness: May impair the patient's ability to operate complex machinery. (5.2)
- HORIZANT is not interchangeable with other gabapentin products. (5.3)
- Suicidal thoughts or behaviors: HORIZANT is a prodrug of gabapentin, an antiepileptic drug (AED). AEDs increase the risk of suicidal thoughts or behaviors. Monitor for suicidal thoughts or behaviors. (5.4)

---------- ADVERSE REACTIONS----------

- RLS: Most common adverse reactions (≥10% and at least 2 times the rate of placebo) were somnolence/sedation and dizziness. (6.1)
- PHN: Most common adverse reactions (≥10% and greater than placebo) were dizziness, somnolence, and headache. (6.1)

FPI: CONTENTS- The following significant changes were noted:

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE: The following significant changes were noted:

1.1 Treatment of Restless Legs Syndrome

HORIZANT® (gabapentin enacarbil) Extended-Release Tablets are indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults.

HORIZANT is not recommended for patients who are required to sleep during the daytime and remain awake at night.

1.2 Management of Postherpetic Neuralgia

HORIZANT (gabapentin enacarbil) Extended-Release Tablets are indicated for the management of postherpetic neuralgia (PHN) in adults.

2 DOSAGE AND ADMINISTRATION: The following significant changes were noted:

Tablets should be swallowed whole and should not be cut, crushed, or chewed.

Tablets should be taken with food.

HORIZANT is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles *[see Warnings and Precautions (5.3)]*.

2.2 Postherpetic Neuralgia

The recommended dosage of HORIZANT is 600 mg twice daily. HORIZANT should be initiated at a dose of 600 mg in the morning for 3 days of therapy, then increased to 600 mg twice daily (1,200 mg/day) on day four. In the 12-week principal efficacy study, additional benefit of using doses greater than 1,200 mg a day was not demonstrated, and these higher doses resulted in an increase in adverse reactions *[see Adverse Reactions (6.1)]*.

If the dose is not taken at the recommended time, skip this dose, and the next dose should be taken at the time of the next scheduled dose.

2.3 Renal Impairment

Dosing of HORIZANT is adjusted in accordance with renal function, as represented by creatinine clearance *[see Clinical Pharmacology (12.3)]*. Target dose regimens are listed in Table 1 and Table 2.

Table 2. Dosage of HORIZANT for Patients With Postherpetic Neuralgia in Accordance With Creatinine Clearance

Creatinine Clearance (mL/min)	Titration	Maintenance	Tapering
≥60	600 mg in AM for 3 days	600 mg twice daily	600 mg in AM for 1 week
30 - 59	300 mg in AM for 3 days	300 mg twice daily. Increase to 600 mg twice daily as needed[a]	Reduce current maintenance dose to once daily in AM for 1 week
15 - 29	300 mg in AM on Day 1 and Day 3	300 mg in AM. Increase to 300 mg twice daily if needed[a]	If taking 300 mg twice daily, reduce to 300 mg once daily in AM for 1 week. If taking 300 mg once daily, no taper needed.
<15	None	300 mg every other day in AM. Increase to 300 mg once daily in AM if needed[a]	None
<15 on hemodialysis	None	300 mg following every dialysis. Increase to 600 mg following every dialysis if needed[a]	None

[a] Based on tolerability and efficacy

In patients with stable renal function, CrCl can be estimated using the equation of Cockcroft and Gault:

for males: CrCl = (140-age)(weight)/[(72)(SCr)]
for females: CrCl = (0.85)(140-age)(weight)/[(72)(SCr)]

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

3 DOSAGE FORMS AND STRENGTHS: There were no changes noted.

4 CONTRAINDICTIONS: There were no changes noted.

5 WARNINGS AND PRECAUTIONS: The following significant changes were noted:

5.2 Somnolence/Sedation and Dizziness

HORIZANT causes somnolence/sedation and dizziness (see Tables 4 and 5). Patients should be advised not to drive a car or operate other complex machinery until they have gained

sufficient experience on HORIZANT to assess whether HORIZANT impairs their ability to perform these tasks.

During the controlled trials in patients with RLS, somnolence/sedation was reported in 20% of patients treated with 600 mg of HORIZANT per day compared with 6% of patients receiving placebo. In those patients treated with HORIZANT who reported somnolence, the somnolence persisted during treatment in about 30%. In the remaining patients, symptoms resolved within 3 to 4 weeks. Dizziness was reported in 13% of patients receiving 600 mg of HORIZANT per day compared with 4% of patients receiving placebo. In those patients treated with HORIZANT who reported dizziness, symptoms persisted during treatment in about 20%. Somnolence/sedation led to withdrawal in 2% of patients receiving 600 mg of HORIZANT per day. Dizziness led to withdrawal in 1% of patients receiving 600 mg of HORIZANT per day. The incidence of these adverse reactions was greater in the patients receiving 1,200 mg per day.

During the 12-week, controlled study in patients with PHN, somnolence was reported in 10% of patients treated with 1,200 mg of HORIZANT per day compared with 8% of patients receiving placebo. Fatigue/asthenia was reported in 6% of patients treated with 1,200 mg of HORIZANT per day compared with 1% of patients receiving placebo. In those patients treated with 1,200 mg of HORIZANT per day who reported somnolence (10%), the somnolence persisted during treatment in about 27%. In the remaining patients, symptoms resolved within 4 to 5 weeks. Dizziness was reported in 17% of patients receiving 1,200 mg of HORIZANT per day compared with 15% of patients receiving placebo. In those patients treated with 1,200 mg of HORIZANT per day who reported dizziness, symptoms persisted during treatment in about 6%. Somnolence led to withdrawal in <1% of patients receiving 1,200 mg of HORIZANT per day compared with 2% of patients receiving placebo. Dizziness led to withdrawal in 2% of patients receiving 1,200 mg of HORIZANT per day compared with 3% of patients receiving placebo.

5.6 Discontinuation of HORIZANT

When discontinuing HORIZANT, patients with RLS receiving 600 mg or less once daily can discontinue the drug without tapering. If the recommended dose is exceeded, the dose should be reduced to 600 mg daily for 1 week prior to discontinuation to minimize the potential of withdrawal seizure.

In patients with PHN receiving HORIZANT twice daily, the dose should be reduced to once daily for 1 week prior to discontinuation to minimize the potential of withdrawal seizure, see Table 2 *[see Dosage and Administration (2.3)]*.

6 ADVERSE REACTIONS: There following significant changes were noted:

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In all controlled and uncontrolled trials across various patient populations, more than 2,300 patients have received HORIZANT orally in daily doses ranging from 600 to 3,600 mg.

Restless Legs Syndrome: The exposure to HORIZANT in 1,201 patients with RLS included 613 exposed for at least 6 months and 371 exposed for at least 1 year. HORIZANT in

the treatment of RLS was studied primarily in placebo-controlled trials (n = 642), and in long-term follow-up studies. The population with RLS ranged from 18 to 82 years of age, with 60% being female and 95% being Caucasian.

The safety of HORIZANT in doses ranging from 600 to 2,400 mg has been evaluated in 515 patients with RLS in 3 double-blind, placebo-controlled, 12-week clinical trials. The 600-mg dose was studied in 2 of the 3 studies. Eleven out of 163 (7%) patients treated with 600 mg of HORIZANT discontinued treatment due to adverse reactions compared with 10 of the 245 (4%) patients who received placebo.

The most commonly observed adverse reactions (≥5% and at least 2 times the rate of placebo) in these trials for the 600-mg dose of HORIZANT were somnolence/sedation and dizziness (see Table 4). Table 4 lists treatment-emergent adverse reactions that occurred in ≥2% of patients with RLS treated with HORIZANT and numerically greater than placebo.

Table 4. Incidence of Adverse Reactions in 12-Week RLS Studies Reported in ≥2% of Patients Treated With 600 or 1,200 mg of HORIZANT and Numerically Greater Than Placebo

Body System/Adverse Reaction	Placebo[a] (N = 245) %	HORIZANT 600 mg/day[b] (N = 163) %	HORIZANT 1,200 mg/day[c] (N = 269) %
Nervous system disorders			
Somnolence/sedation	6	20	27
Dizziness	4	13	22
Headache	11	12	15
Gastrointestinal disorders			
Nausea	5	6	7
Dry mouth	2	3	4
Flatulence	<1	3	2
General disorders and administration site conditions			
Fatigue	4	6	7
Irritability	1	4	4
Feeling drunk	0	1	3
Feeling abnormal	<1	<1	3
Peripheral edema	1	<1	3
Metabolism and nutritional disorders			
Weight increased	2	2	3
Increased appetite	<1	2	2
Ear and labyrinth disorders			
Vertigo	0	1	3
Psychiatric disorders			
Depression	<1	<1	3
Libido decreased	<1	<1	2

[a] Placebo was a treatment arm in each of the 3 double-blind, placebo-controlled, 12-week clinical trials.

[b] The 600-mg dose of HORIZANT was a treatment arm in 2 of the 3 double-blind, placebo-controlled, 12-week clinical trials.

[c] The 1,200-mg dose of HORIZANT was a treatment arm in each of the 3 double-blind, placebo-controlled, 12-week clinical trials.

Adverse reactions reported in these three 12-week studies in <2% of patients treated with 600 mg of HORIZANT and numerically greater than placebo were balance disorder, blurred vision, disorientation, feeling drunk, lethargy, and vertigo.

The following adverse reactions were dose-related: somnolence/sedation, dizziness, feeling drunk, libido decreased, depression, headache, peripheral edema, and vertigo.

Postherpetic Neuralgia: The exposure to HORIZANT in 417 patients with PHN included 207 patients exposed for at least 3 months. Overall, the mean age of patients in the PHN studies ranged from 61 to 64 years of age across dose groups; the majority of patients were male (45% to 61%) and Caucasian (80% to 98%).

The safety of HORIZANT in doses ranging from 1,200 to 3,600 mg has been evaluated in 417 patients with PHN in 3 clinical studies. The principal efficacy study evaluating the efficacy and safety of HORIZANT in the management of PHN was a 12-week, double-blind, multicenter study comparing 1,200 mg/day, 2,400 mg/day and 3,600 mg/day to placebo. Six out of 107 (6%) patients treated with 1,200 mg of HORIZANT discontinued treatment due to adverse events compared with 12 of the 95 (13%) patients who received placebo.

The most commonly observed adverse reactions (≥10% and greater than placebo) in this trial for the 1,200 mg dose of HORIZANT were dizziness, somnolence and headache (see Table 5). Table 5 lists treatment-emergent adverse reactions that occurred in ≥2% of patients with PHN treated with HORIZANT 1,200 mg/day and numerically greater than placebo.

Table 5. Incidence of Adverse Reactions (in At Least 2% of Patients Treated With 1,200 mg/day of HORIZANT and Numerically Greater Than the Placebo Rate) Reported in All Patients in the 12-Week PHN Study

	Percent of patients			
Body System/Adverse Reaction	Placebo (N = 95)	HORIZANT 1,200 mg/day (N = 107)	HORIZANT 2,400 mg/day (N = 82)	HORIZANT 3,600 mg/day (N = 87)
Nervous System				
Dizziness	15	17	26	30
Somnolence	8	10	11	14
Headache	9	10	10	7
Gastrointestinal disorders				
Nausea	5	8	4	9
General disorders and administration site conditions				
Fatigue/Asthenia	1	6	4	10
Peripheral edema	0	6	7	6
Psychiatric disorders				
Insomnia	2	3	5	7
Metabolism and nutritional disorders				
Weight increased	1	3	5	5
Eye disorders				
Blurred vision	0	2	5	2

The following adverse reactions were also reported as ≥2% at 2,400 mg/day and/or 3,600 mg/day and appeared to be dose-related but were <2% at 1,200 mg/day: balance disorder, confusional state, depression, dry mouth, flatulence, increased appetite, irritability, and vertigo. Dizziness, somnolence, fatigue, and insomnia appeared to show a dose relationship.

7 DRUG INTERACTIONS: There were no changes noted.

8 USE IN SPECIFIC POPULATIONS: **The following significant changes were noted:**

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies with HORIZANT in pregnant women. In nonclinical studies in rat and rabbits, administration of gabapentin enacarbil was developmentally toxic when administered to pregnant animals at doses and gabapentin exposures greater than those used clinically. HORIZANT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When pregnant rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or 5,000 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was increased at the 2 highest doses and fetal body weights were decreased at the high dose. The no-effect dose for embryo-fetal developmental toxicity in rats (200 mg/kg/day) represents approximately

2 times the gabapentin exposure associated with the maximum recommended human dose (MRHD) of 1,200 mg/day gabapentin enacarbil on an area under the curve (AUC) basis.

When pregnant rabbits were administered gabapentin enacarbil (oral doses of 200, 500, or 2,500 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was increased and fetal body weights were decreased at the high dose. The no-effect dose for embryo-fetal developmental toxicity in rabbits (500 mg/kg/day) represents approximately 9 times the gabapentin exposure associated with the MRHD of 1,200 mg/day gabapentin enacarbil on an AUC basis.

When female rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or 5,000 mg/kg/day) throughout the pregnancy and lactation periods, offspring growth and survival were decreased at the two highest doses. The no-effect dose for pre- and post-natal developmental toxicity in rats is approximately 2 times the MRHD on an AUC basis.

In reproductive and developmental studies of gabapentin, developmental toxicity was observed at all doses tested. Increased incidences of hydroureter and/or hydronephrosis were observed in rat offspring following treatment of pregnant animals in studies of fertility and general reproductive performance, embryo-fetal development, and peri- and post-natal development. Overall, a no-effect dose was not established. In mice, treatment of pregnant animals with gabapentin during the period of organogenesis resulted in delayed fetal skeletal ossification at all but the lowest dose tested. When pregnant rabbits were treated with gabapentin during the period of organogenesis, an increase in embryo-fetal mortality was observed at all doses of gabapentin tested.

In a published study, gabapentin (400 mg/kg/day) was administered by intraperitoneal injection to neonatal mice during the first postnatal week, a period of synaptogenesis in rodents (corresponding to the last trimester of pregnancy in humans). Gabapentin caused a marked decrease in neuronal synapse formation in brains of intact mice and abnormal neuronal synapse formation in a mouse model of synaptic repair. Gabapentin has been shown *in vitro* to interfere with activity of the $\alpha 2\delta$ subunit of voltage-activated calcium channels, a receptor involved in neuronal synaptogenesis. The clinical significance of these findings is unknown.

8.5 Geriatric Use

Of the 515 patients treated with HORIZANT in the 3 double-blind, placebo-controlled, 12-week clinical trials for RLS, 11% were 65 to 74 years of age and 1% were 75 years of age and older. Clinical trials of HORIZANT for the treatment of RLS did not include a sufficient number of patients 65 years and older to determine whether they respond differently from younger individuals.

In the 12-week, double-blind, placebo-controlled study of HORIZANT for the management of PHN (n=276 patients treated with HORIZANT), 37% were 65 to 74 years of age and 13% were 75 years of age and older. The overall incidence of adverse events was comparable between the patients aged ≥18 to <65 years and ≥65 to <74 years. No overall differences in the safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Gabapentin is known to be almost exclusively excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, the frequency of dosing may

need to be adjusted based on calculated creatinine clearance in these patients *[see Dosage and Administration (2.3)]*.

9 DRUG ABUSE AND DEPENDENCE: The following language was added

9.1 Controlled Substance

HORIZANT, a prodrug of gabapentin, is not a scheduled drug.

9.2 Abuse

Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta or kappa), or cannabinoid 1 receptor sites. A small number of postmarketing cases report gabapentin misuse and abuse. These individuals were taking higher than recommended doses of gabapentin for unapproved uses. Most of the individuals described in these reports had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances.

When prescribing products that deliver gabapentin, carefully evaluate patients for a history of drug abuse and observe them for signs and symptoms of gabapentin misuse or abuse (e.g. development of tolerance, self dose escalation, and drug-seeking behavior).

9.3 Dependence

There are rare postmarketing reports of individuals experiencing withdrawal symptoms shortly after discontinuing higher than recommended doses of gabapentin used to treat illnesses for which the drug is not approved. Such symptoms included agitation, disorientation, and confusion after suddenly discontinuing gabapentin that resolved after restarting gabapentin. Most of these individuals had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances. The dependence and abuse potential of gabapentin has not been evaluated in human studies.

10 OVERDOSAGE: **There were no changes noted.**

11 DESCRIPTION: **There were no changes noted.**

12 CLINICAL PHARMACOLOGY: The f**ollowing significant changes were noted:**

12.1 Mechanism of Action

Gabapentin enacarbil is a prodrug of gabapentin and, accordingly, its therapeutic effects in RLS and PHN are attributable to gabapentin.

The precise mechanism by which gabapentin is efficacious in RLS and PHN is unknown.

The mechanism of action by which gabapentin is efficacious in PHN is unknown but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test), but does not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to human pain is not known.

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. Gabapentin enacarbil and gabapentin have been tested in radioligand binding assays, and neither exhibited affinity for a number of other common receptor, ion channel, or transporter proteins.

In vitro studies have shown that gabapentin binds with high affinity to the α2δ subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of gabapentin enacarbil in RLS and PHN is unknown

13 NONCLINICAL TOXICOLOGY: **The following changes were note:**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Oral (gavage) carcinogenicity studies were conducted in mice and rats. In mice, gabapentin enacarbil was tested at doses of 500, 2,000, or 5,000 mg/kg/day for up to 104 weeks. There was no evidence of drug-related carcinogenicity. The highest dose tested is 16 times the MRHD of 1,200 mg/day, on a plasma AUC basis.

In rats, gabapentin enacarbil was tested at doses of 500, 2,000, or 5,000 mg/kg/day for up to 97 weeks in mid-dose males, 90 weeks in high-dose males, and 104 weeks in females. The plasma exposures (AUC) for gabapentin at these doses are approximately 4, 17, and 37 times, respectively, that in humans at the MRHD. Increases in the incidence of pancreatic acinar adenoma and carcinoma were found in mid-dose males and high-dose males and females.

In 2-year dietary carcinogenicity studies of gabapentin, no evidence of drug-related carcinogenicity was observed in mice treated at doses up to 2,000 mg/kg/day. In rats, increases in the incidence of pancreatic acinar cell adenoma and carcinoma were found in male rats receiving the highest dose (2,000 mg/kg), but not at doses of 250 or 1,000 mg/kg/day. At 1,000 mg/kg/day, the plasma AUC for gabapentin is estimated to be approximately 13 times that in humans at the MRHD.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and thus may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including human.

Mutagenesis: Gabapentin enacarbil was negative in *in vitro* bacterial reverse mutation (Ames) and *in vivo* rat micronucleus assays. In an *in vitro* human lymphocyte assay, there was an increase in the number of chromosomal aberrations with gabapentin enacarbil. This *in vitro* response was attributed to acetaldehyde released by hydrolysis of gabapentin enacarbil during the incubation period. Acetaldehyde is known to cause chromosome aberrations *in vitro*, but is readily metabolized *in vivo*. The small quantity of acetaldehyde formed from gabapentin enacarbil *in vivo* is rapidly cleared by normal metabolic activity.

Impairment of Fertility: Oral administration of gabapentin enacarbil (doses of 0, 200, 1,000, or 5,000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females up to day 7 of gestation resulted in no adverse effects on fertility. The highest dose tested is approximately 39 times the MRHD on an AUC basis.

14 CLINICAL STUDIES: The following significant changes were noted:

14.2 Postherpetic Neuralgia (PHN) 12-Week Study

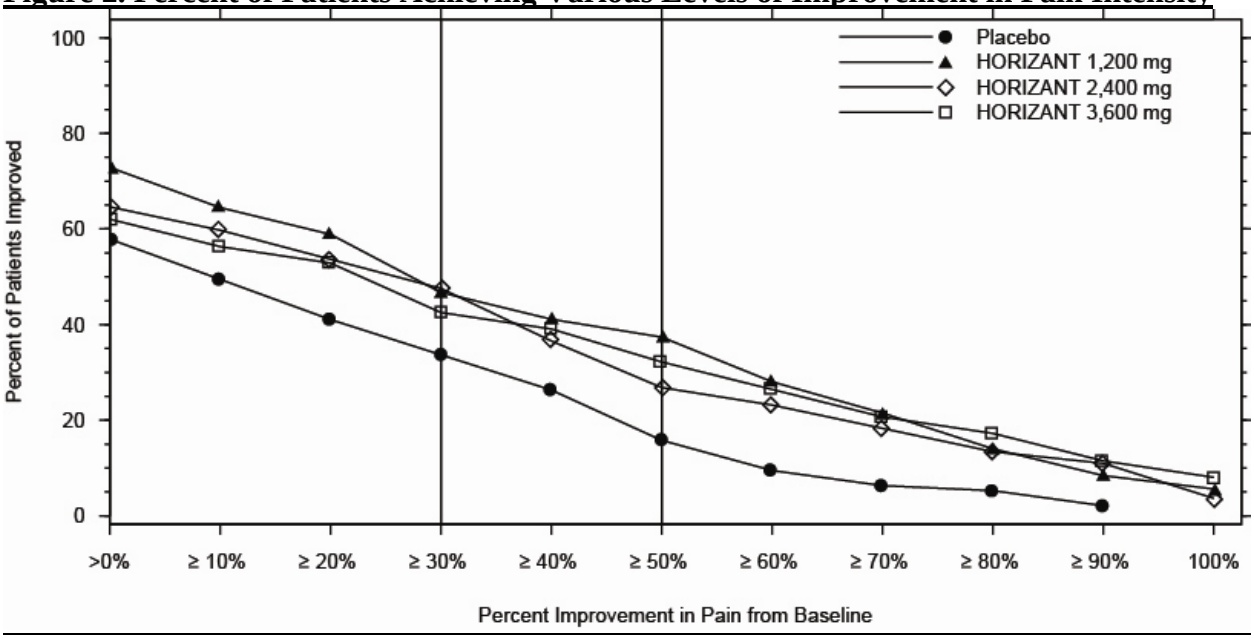
The efficacy of HORIZANT for the management of postherpetic neuralgia was established in a multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-week study evaluating the efficacy, safety, and dose response of 3 maintenance doses of HORIZANT (1,200, 2,400, and 3,600 mg/day, with 107, 82, and 87 patients in each dosing group, respectively). Patients greater than 18 years of age with a documented medical diagnosis of PHN of at least three months duration were enrolled. To ensure that patients had significant pain, randomized patients were required to have a minimum baseline 24-hour average Pain Intensity Numerical Rating Scale (PI-NRS) intensity score of at least 4.0 on the 11-point numerical PI-NRS, ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine").

In this study, a total of 276 patients received HORIZANT while 95 patients received placebo. Following a 1 week baseline period during which patients were screened for eligibility, patients began a 1 week up-titration period followed by a 12-week maintenance treatment period, and then a 1 week down-titration period.

Treatment with HORIZANT statistically significantly improved the mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline at all doses tested. A benefit over placebo was observed for all 3 doses of HORIZANT as early as Week 1 and maintained to the end of treatment. Additional benefit of using doses of greater than 1,200 mg a day was not demonstrated.

For various degrees of improvement in pain from baseline to end of maintenance treatment, Figure 2 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement.

Figure 2. Percent of Patients Achieving Various Levels of Improvement in Pain Intensity



16 HOW SUPPLIED/STORAGE AND HANDLING: There were no changes noted.

17 PATIENT COUNSELING INFORMATION: The following significant changes were noted:

17.6 Dosing Instructions

- Patients should be instructed to take HORIZANT only as prescribed.
- Tablets should be swallowed whole and should not be cut, crushed, or chewed.
- Tablets should be taken with food.
- For Restless Legs Syndrome, 600 mg HORIZANT should be taken once daily at about 5 PM. If the dose is not taken at the recommended time, the patient should take the next dose at about 5 PM the following day.
- For Postherpetic Neuralgia, the starting dose is 600 mg HORIZANT in the morning for 3 days. Starting on day 4, 600 mg HORIZANT should be taken twice daily. If the dose is not taken at the recommended time, the next dose should be taken at the time of next scheduled dose.
- Patients should be instructed about how to discontinue HORIZANT.

MEDICATION GUIDE: The following significant changes were noted:

What is HORIZANT?

HORIZANT is a prescription medicine used to treat adults with:

- moderate-to-severe primary Restless Legs Syndrome (RLS).
- pain from damaged nerves (postherpetic pain) that follows healing of shingles (a painful rash that comes after a herpes zoster infection).

HORIZANT is not for people with RLS who need to sleep during the daytime and need to stay awake at night.

HORIZANT is not the same medicine as gabapentin (for example, NEURONTIN® or GRALISE®) and should not be used in its place.

What should I tell my healthcare provider before taking HORIZANT?

Before taking HORIZANT, tell your healthcare provider if you:

- have or have had kidney problems or are on hemodialysis.
- have or have had depression, mood problems, or suicidal thoughts or behavior.
- have or have had seizures.
- have a history of drug abuse
- have any other medical conditions
- if you are pregnant or plan to become pregnant. It is not known if HORIZANT will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become

pregnant while taking HORIZANT. You and your healthcare provider will decide if you should take HORIZANT while you are pregnant.
- are breastfeeding or plan to breastfeed. Your body turns HORIZANT into another drug (gabapentin) that passes into your milk. It is not known if this can harm your baby. You and your healthcare provider should decide if you will take HORIZANT or breastfeed.

How should I take HORIZANT?

- Take HORIZANT exactly as your healthcare provider tells you to take it. Your healthcare provider will tell you how much HORIZANT to take and when to take it.
- Take HORIZANT tablets whole. **Do not** cut, crush, or chew your tablet.
- Take HORIZANT tablets with food.
- **Do not stop taking HORIZANT without talking to your healthcare provider first.** If you stop taking HORIZANT suddenly, you may develop side effects.
- If you forget to take your medicine at the time recommended by your healthcare provider, just skip the missed dose. Take the next dose at your regular time. **Do not** take 2 doses at one time.
- If you take too much HORIZANT, call your healthcare provider or go to the nearest hospital emergency room right away.

Recommendations

The above additions to the Package Insert and Medication Guide have been found acceptable to the Sponsor and the Division and will be incorporated in the final approved version of labeling for NDA 022399/s-003

Sharon Turner-Rinehardt
Senior Regulatory Health Project Manager

Supervisory Comment/Concurrence:

6/3/2012

Sara Stradley, M.S.
Chief, Project Management Staff

Drafted: STR/060112
Revised/Initialed:
CSO LABELING REVIEW

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

/s/

SHARON M TURNER RINEHARDT
06/04/2012

SARA E STRADLEY
06/05/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 22399 BLA#	NDA Supplement #:S- 003 BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Horizant Established/Proper Name: Gabapentin Enacarbil Dosage Form: Extended Release Tablets Strengths: 600 mg		
Applicant: Glaxo Group Ltd Agent for Applicant (if applicable):		
Date of Application: August 9, 2011 Date of Receipt: August 9, 2011 Date clock started after UN:		
PDUFA Goal Date: June 9, 2012	Action Goal Date (if different): June 4, 2012	
Filing Date: October 8, 2011	Date of Filing Meeting: September 22, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Management of postherpetic neuralgia		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☒ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 68341	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?		X		
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*: August 31, 2011	X			Scheduling proposal will be requested in 74-day letter.

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			X	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***			X	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***	X			Modification to the MG was made for this supplement.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			X	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** March 17, 2011 ***If yes, distribute minutes before filing meeting***	X			Pre-NDA
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 22, 2011

BLA/NDA/Supp #: NDA 22399/s-003

PROPRIETARY NAME: Horizant

ESTABLISHED/PROPER NAME: Gabapentin Enacarbil

DOSAGE FORM/STRENGTH: Extended Release Tablets

APPLICANT: GlaxoSmithKline

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Management of postherpetic neuralgia

BACKGROUND: The sponsor submitted a 50(b)(2) supplemental NDA for postherpetic neuralgia. The Division of Neurology Products approved the original NDA on April 6, 2011 for restless leg syndrome.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	S. Turner-Rinehardt	Y
	CPMS/TL:	S. Stradley	N
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	R. Levin	N
	TL:	F. Pucino	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	W. Qiu	Y
	TL:	Y. Xu	Y
Biostatistics	Reviewer:	K. Meaker	Y
	TL:	D. Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	A. Emami	Y
	TL:	A. Wasserman	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	B. Ho	Y
	TL:	R. Raghavachari	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	S. Sun	Y
	TL:	M. Klein	N
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Rigoberto Roca

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

SHARON M TURNER RINEHARDT
05/21/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DPDP)
Division of Consumer Drug Promotion (DCDP)

****Pre-decisional Agency Information****

Memorandum

Date: May 4, 2012

To: Sharon Turner-Rinehardt, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Samuel M. Skariah, Regulatory Review Officer, DPDP
L. Shenee Toombs, Regulatory Review Officer, DCDP

CC: Lisa Hubbard, Group Leader, DPDP
Shefali Doshi, Group Leader, DCDP

Subject: NDA #022399/s-003
Horizant (gabapentin enacarbil) Labeling Review

OPDP has reviewed the proposed package insert (PI) and Medication Guide (Med Guide) for Horizant originally consulted from DMEP to OPDP on April 5, 2012.

Comments regarding the PI and Med Guide are provided in the marked versions below.

Thank you for the opportunity to comment on these proposed materials.

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/s/

SAMUEL M SKARIAH
05/07/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	April 23, 2012
To:	Bob A. Rappaport, MD Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	DMPP Review of Patient Labeling (Medication Guide)
Drug Name (established name):	HORIZANT (gabapentin enacarbil)
Dosage Form and Route:	Extended-Release Tablets
Application Type/Number:	NDA 22-399
Supplement number:	S-003
Applicant:	GlaxoSmithKline
OSE RCM #:	2011-3472

1 INTRODUCTION

On August 9, 2011, GlaxoSmithKline submitted for the Agency's review an Efficacy Prior Approval Supplement (PAS) to their approved 505 (b) (2) New Drug Application, NDA 22-399/S-003, Horizant (gabapentin enacarbil) Extended-Release Tablets. Horizant (gabapentin enacarbil) Extended-Release Tablets was approved by the Agency for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) on April 6, 2011. This PAS proposes a new indication for management of postherpetic neuralgia (PHN) in adults. On September 20, 2011, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for Horizant (gabapentin enacarbil) Extended-Release Tablets.

This review is written in response to a request by the DAAAP for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG), for HORIZANT (gabapentin enacarbil) Extended-Release Tablets.

2 MATERIAL REVIEWED

- Draft HORIZANT (gabapentin enacarbil) Extended-Release Tablets Medication Guide (MG) received August 9, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on April 9, 2012.
- Draft HORIZANT (gabapentin enacarbil) Extended-Release Tablets Prescribing Information (PI) received August 9, 2011, revised by the Review Division throughout the current review cycle, and received by DMPP on April 9, 2012.
- Approved Neurontin (gabapentin) Capsules, Tablets, and Oral Solution comparator labeling dated August 10, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG, we have:

- performed a focused review of the revisions identified in the PI and MG

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
04/23/2012

BARBARA A FULLER
04/23/2012

LASHAWN M GRIFFITHS
04/23/2012

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 21, 2012

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

CC: Russell Katz, MD, Director
Division of Neurology Products (DNP)

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Stephen Sun, MD, Medical Officer
Controlled Substance Staff

Subject: Gabapentin enacarbil (NDA022399 for restless leg syndrome; IND068341for post-herpetic neuralgia)
505B2: Gabapentin (20-235, 20-882, 21-129, 21-216, 21-397, 21-424)
Indication: Post-herpetic neuralgia; Restless leg syndrome
Dosages: 300mg, 600mg
Sponsor: GlaxoSmithKline

Materials reviewed:
1. Dormitzer C, Chai G, Greene P, Goulding MR. Review of drug utilization and DAWN ED visits related to Products – Review of abuse-related events with gabapentin and pregabalin (NDA# 20-235, 20-882, 21-129, 21-216, 21-397, 21-424. FDA Internal Memorandum. July 15, 2011.
2. Pfizer. NDA 20-235. Labeling Supplement. Item 3 – Summary. 3.11 Abuse Liability/Overdosage. 2002.
3. Sun S, Klein M. Internal Memorandum – GSK1838262 (Gabapentin Enacarbil ER / HORIZANT). March 21, 2011.
4. Winiarski A, Choi L. Pharmacovigilance Data Provision – Gabapentin enacarbil ER (Horizant), gabapentin (Neurontin), pregabalin (Lyrica).
5. GSK. Responses to 21 October 2011 FDA Requests for Information Regarding Abuse Potential. (m1.11.4 Informawtion Amendment).
6. GSK. (b) (4) of Gabapentin Enacarbil. (m.11.4 (b) (4) of Gabapentin Enacarbil).

Table of Contents

I. Summary

A. Background

This followup memorandum concerns abuse liability issues for gabapentin that relate to the analysis and recommendations for GSK's 505(b)(2) application for Horizant® (gabapentin enacarbil) based upon the initial consult via IND068341 for post-herpetic neuralgia (and now as an efficacy supplement to NDA022399).

The FDA Division of Drug Risk Evaluation (Pharmacovigilance) in 2004 performed a safety review of gabapentin (Neurontin®) during the approval review of a related drug, pregabalin.[1] At that time, the review showed that the postmarketing cases contained limited information related to abuse; as such, DDRE made no recommendations for changing the label regarding abuse liability (no abuse and dependence information). In this updated 2012 review, 8 additional years of gabapentin postmarketing experience, sections containing abuse liability information from the 2002 gabapentin application, postmarketing experience from the approval of Horizant (NDA022399), and the Sponsor's efficacy supplement for post-herpetic neuralgia materials were reviewed.

B. Conclusions:

1. FDA conducted a prior surveillance of gabapentin's postmarketing abuse liability profile in 2004. The present review is an update by the Controlled Substance Staff that includes an additional 8 years of postmarketing experience from various sources such as Drug Abuse Warning Network (DAWN), Adverse Event Report System (AERS), American Association of Poison Control Center (AAPCC), Horizant postmarketing experience, literature, and abuse message board postings. In general, the rate of gabapentin misuse and abuse appears to be relatively low when considering the large denominator of prescriptions ((b) (4) in 2010) and doses

[1] Thambi L. Drug: Gabapentin (Neurontin®) NDA# 20-235, 20-882, 21-129, 21-216, 21-397, 21-424. Reaction: abuse. Internal memorandum. Sept 17, 2004.

when compared to other scheduled drugs of abuse. Of note, according to some metrics, the abuse numerators are of the same order of magnitude as that of pregabalin, which is listed in Schedule V of the Controlled Substances Act (CSA). However, there are numerous confounders in the interpretation of each source data set, the following is a summary of the findings:

a. A 2004 FDA review of data from December 1993 to 2004 identified 96 AERS cases: withdrawal (36), drug seeking behavior (22), euphoria (19), addiction (18), and abuse (1). Because the assessment was difficult to determine due to confounding information, no label changes were recommended at the time of review.

b. Drug Abuse Warning Network (DAWN): A 2011 FDA review of data covering years 2006 to 2009 showed comparable DAWN abuse ratios of all misuse and abuse (ALLMA) emergency department visits per 10,000 prescriptions between gabapentin and pregabalin. However, DAWN does not delineate substance by causality and gabapentin, from other indicators, is associated with polypharmacy use and misuse. Gabapentin is a common appropriately-prescribed pharmaceutical adjunct for pain management and other non-approved medical indications. The data shows the following for years 2006, 2007, 2008, 2009, respectively:

   (1) (gabapentin) 3.9, 3.5, 4.7, 5.7 per 10,000 prescriptions
   (2) (pregabalin) 4.7, 2.9, 6.4, 4.3 per 10,000 prescriptions

   (3) (gabapentin) 4.1, 3.7, 4.9, 5.8 per 1,000,000 pills
   (4) (gabapentin) 7.4, 4.3, 9.4, 6.1 per 1,000,000 pills

c. Adverse Event Reporting System (AERS): Cases from AERS are spontaneously-reported and do have a precise denominator; therefore, values cannot be used for direct rate comparisons but provide insight on occurrence. Abuse-related AERS cases, using the drug abuse, dependence, and withdrawal MedDRA SMQ query for 2005, 2006, 2007, 2008, 2009, 2010, 2011-1H showed relatively similar reported number of cases between gabapentin and pregabalin, respectively:

   (1) (gabapentin-only) 9, 17, 9, 5, 20, 18
   (2) (gabapentin and other drugs) 85, 106, 73, 58, 86, 88

   (3) (pregabalin only) 22, 17, 18, 6, 74, 37
   (4) (pregabalin and other drugs) 68, 75, 88, 53, 189, 108, respectively.

d. American Association of Poison Control Center (AAPCC): The majority of reported fatalities to poison control centers are polypharmacy, related to intentional suicides, and causality-ranking showing gabapentin as not the most suspect drug (opioids, antidepressants, and anxiolytics were primary). Since gabapentin has been prescribed according to approved indications and unapproved uses, causality to the fatalities is difficult to assess as these may also be used legitimately as adjuncts to opioids and other drugs for pain management. The number of fatality mentions in the American Association of Poison Control Center's Annual Poison Control reports for years 2005, 2006, 2007, 2008, 2009 showed relatively similar, though small, values between gabapentin and pregabalin, respectively:

(1) (gabapentin) 11, 20, 21, 12, 19
(2) (pregabalin) 0, 10, 9, 14, 4

e. Postmarketing Horizant experience: As reported in the period safety reports for the past 9 months following approval for its use in restless leg syndrome, rare adverse-event related cases have included some non-alert reports (more than 2 case reports) of feeling abnormal, dizziness, hypersomnia, psychomotor hyperactivity, sedation, somnolence, abnormal dreams, confusional state, hallucination, and insomnia.

f. Published literature: Published articles include a few case reports of gabapentin withdrawal symptoms (symptoms reversible after gabapentin was re-initated) and abuse behaviors (high-dose intoxication with and without concomitant use of other illicit and legitimate drugs).

g. Abuse message board postings: In well-known internet-based, abuse-related message boards (Bluelight and Erowid), several postings on the effects of gabapentin abuse show an inconsistent profile that span a wide range including: euphoria, depression, sedation, anxiolysis, stimulation, dissociation, hallucinogenesis, somnogenesis, and elation. While none of the postings referenced Horizant® directly, other highlights of gabapentin abuse include:

(1) Reported dose range of abuse: 300 mg to 9000
(2) Used in combination with other legal and illicit substances
(3) Pregabalin, as a related compound, likely to have a more potent effect
(4) Perceived as having a greater safety margin (more difficult to overdose)
(5) Used for mitigating withdrawal symptoms of commonly abused drugs
(6) Attempted potentiation by drinking with soda
(7) Variable experience reported by the same person

2. The Sponsor's proposed [redacted] (b) (4)

3. The abuse potential section from the original 2002 gabapentin application was not reviewed and the present label information reflects the legacy evaluation of its abuse potential by Pfizer, Sponsor of the reference listed drug, gabapentin. The highlights are as follows:
   a. According to Pfizer (the holders of the 505(b)(2) reference drug, Neurontin (gabapentin), receptor binding studies did not indicate affinities to the common drugs of abuse receptors.
   b. According to Pfizer, conditioned place preference/drug discrimination studies in rats did not show evidence of reinforcement or generalization to known drugs of abuse.
   c. According to Pfizer, locomotor study in rats did not show similarity to stimulant activity.
   d. Human abuse potential studies of gabapentin in experienced abusers were not performed.
   e. Clinical adverse event review indicated 2 of 820 patients in the 3600 mg/day treatment group experienced euphoria versus 0 of 537 patients for placebo.
   f. Clinical pharmacology studies indicated (Study 945-190) 2 subjects at 2400 mg/day, 4 subjects at the 3600 mg/day, and 1 subject at the 4800 mg/day dose experienced euphoria and (Study 945-057) 1 subject in the 1800 mg/day treatment group of 24 experienced feeling high.
   g. At an estimated exposure of [redacted] (b) (4) patients (Dec 2000), 24 cases of drug dependence and 36 cases of euphoria were considered. Of the 24 cases, 8 cases were determined to be potentially associated with gabapentin dependence or addiction, 2 cases described reports of drug-seeking behavior, and 1 case of off-label use of gabapentin to abate the withdrawal effects of cocaine (8 of 9,038 adverse event cases reported in the gabapentin postmarketing database).

4. In conclusion, the abuse potential of gabapentin enacarbil is presently not well understood. The subjective effects of the drug in individuals likely to abuse the drug is typically gathered from a human abuse potential study that is conducted on new molecular entities and is described in the draft FDA Guidance on Abuse Potential Assessment. As a comparator, a human abuse potential study was conducted on pregabalin and served as the basis for drug scheduling, but has not been performed for either gabapentin or GEn.

C. **Recommendations:**

1. Continue surveillance of the misuse and abuse of these products (gabapentin, pregabalin, and gabapentin enacarbil) for two to five more years consistent with OSE's recommendation.

2. Label should reflect what is currently known on the abuse and dependence potential of gabapentin enacarbil. Such language should include the summary of postmarketed human experience with gabapentin. For example, the label should include the following:

9.1 Controlled Substance

Gabapentin enacarbil is not a scheduled drug.

9.2 Abuse

(b) (4)

9.3 Dependence

(b) (4)

II. Review

A. **Chemistry**

1. **Product description**

a. Gabapentin is a member of a class of compounds that also includes pregabalin which is characterized by binding to the alpha-2-delta protein that is found within the CNS neuronal tissues. The mechanism of action is not fully understood but involves branched-chain amino acids and chemical analogues of gamma-aminobutyric acid (GABA); however, neither drug has activity in the GABAergic neuronal systems.[2] As a result of its functional similarity, pregabalin ($C_8H_{17}NO_2$)

[2] Bockbrader HN, Wesche D, Miller R et al. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet. 2010. 49(10): 661-9.

and gabapentin ($C_9H_{17}NO_2$) may also share a comparable abuse/non-abuse potential profile. Prior regulatory review of pregabalin, which considered the 2004 OSE review of gabapentin abuse epidemiology, concluded with the final recommendation of Schedule V in the Controlled Substances Act (CSA).[3,4]

b. Gabapentin is approved for postherpetic neuralgia and epilepsy.[5] Gabapentin off-label use was reported in a variety of conditions, including: bipolar disorder, neuropathic pain, diabetic neuropathy, complex regional pain syndrome, attention deficit disorder, restless legs syndrome, trigeminal neuralgia, periodic limb movement disorder of sleep, migraine, and drug and alcohol withdrawal seizures.[6] It is unknown whether the diverse indications of use could contribute to its misuse, abuse, and dependence profile.

B. Pharmacology of drug substance and active metabolites

1. In vitro studies

a. Functional assays

(1) Source data was not available for review.

b. Receptor binding studies

(1) Information on binding of gabapentin to receptors associated with common drugs of abuse are provided by the Sponsor in the Neurontin® (gabapentin) NDA supplement, NDA# 20-235, Item #3 - Summary. 2002 (see Figure 1).

[3] Throckmorton DC. Scheduling recommendation for pregabalin. Memorandum. Dec 21, 2004.
[4] 21CFR1308.15 Schedule V. (a) Schedule V shall consist of the drugs and other substances, by whatever official name, common or usual name, chemical name, or brand name designated, listed in this section. (e) Depressants. Unless specifically exempted or excluded or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a depressant effect on the central nervous system, including its salts: (2) Pregabalin [(S)-3-(aminomethyl)-5-methylhexanoic acid]--2782

[5] Teva Pharmaceuticals USA. Gabapentin Capsules. Product Information. (Sellersville, PA). Revised 10/2010.
[6] Mack A. Examination of the evidence for off-label use of gabapentin. J Managed Care Pharm. 2003. 9(6): 559-68.

Figure 1: Properties of Gabapentin and other Drugs of Abuse Provided by the Sponsor

Drug or Drug Class	**Cellular or Molecular Target**	**Gabapentin Activity**
Gabapentin	^{3}H-Gabapentin binding K^{+}-induced transmitter release GABA transporter trafficking	Radioligand IC50 = 80 nM IC_{50} = 9 µM IC_{50} =< 30 µM EC_{50} = 30 µM
Opioids (analgesics and Anesthetics)	Opiate mu Receptor Agonist	Not Active - mu, delta, kappa receptor binding; no naloxone reversibility
Sedative-Hypnotics and Anxiolytics	Allosteric Enhancement of $GABA_A$ Response	Not Active - [^{3}H] flunitrazepam binding neutron electrophysiology; no flumazenil reversibility
Cocaine, Amphetamines and other Central nervous System Stimulants	Block Dopamine Uptake	Not Active - Dopamine, serotonin or noradrenaline uptake
Hallucinogens, Phenycyclidine, and Similar Agents	NMDA Block or Serotonin Agonist Activity	Not Active - NMDA, phenycyclidine, glycine, serotonin-1 or serotonin-2 radioligand sites
		Not Active - NMDA tissue slice pharmacology, long-term potentiation or NMDA-dependent neuronal Ca influx
Cannabinoids (Marjuana and Related Compounds)	Cannabinoid Receptor Binding	Not Active - Cannabinoid radioligand binding
Nicotine-Like Drugs	Nicotinic Receptor Binding	Not Active - Nicotonic radioligand binding

2. **Safety pharmacology findings**
   (1) Source data was not available for review.

3. **Animal behavioral studies**
   a. Self-administration studies
   (1) Source data was not available for review.

b. Conditioned place preference and drug discrimination study

(1) A preclinical drug discrimination and conditioned place preference study for gabapentin is included in the Neurontin® (gabapentin) NDA supplement, NDA# 20-235, Item #3 - Summary. 2002. In Section 3.11.2.2.1 (Morphine Drug Discrimination and Conditioned Place Preference in Rats). The rationale for morphine as the positive control was not provided other than a statement noting positive CPP results when morphine is compared against saline and known assumptions that rodents demonstrate CPP for mu-opiate agonists, cocaine, amphetamines, ethanol, benzodiazepines, nicotine, and testosterone (in male animals). Information regarding the basis for dose selection, the length of the pretreatment period, and the number of animals tested was not available for review. Sponsor provides the following:

> *"Gabapentin has been tested in the conditioned place preference (CPP) paradigm. This experimental model in rats tests whether, when allowed free access between 2 chambers with different contextual cues (floor texture, visual pattern of walls, etc), the animals will spend more time in the chamber previously associated with morphine administration than in the chamber associated with saline administration. Conditioned place preference in rodents occurs with mu-opiate agonists, cocaine, amphetamines, ethanol, benzodiazepines, nicotine, and testosterone (in male animals).*
>
> *Gabapentin (10, 30, or 100 mg/kg PO) failed to induce CPP in a study in which morphine (0.75 mg/kg SC) caused a prominent and significant place preference. Instead, co-administration of 100 mg/kg gabapentin with morphine reduced the morphine-induced conditioned place preference in comparison to that with morphine alone. Morphine also enhanced dopamine levels in the nucleus accumbens, a region known to be important for the rewarding properties of morphine, whereas gabapentin (100 mg/kg) prevented the morphine-induced increase in dopamine levels in the nucleus accumbens. These results are consistent with a rewarding effect of morphine, but not gabapentin, administration in rats. If anything, gabapentin may reduce the rewarding effect of morphine in rats."*

c. Psychomotor tests

(1) A preclinical locomotor study for gabapentin is included in the Neurontin® (gabapentin) NDA supplement, NDA# 20-235, Item #3 - Summary. 2002. In Section 3.11.2.2.2 (Effect of Gabapentin on Increased Locomotor Activity from Administration of Cocaine or Amphetamine), Sponsor provides the following:

Oral dosing of gabapentin (10, 30, or 100 mg/kg) prior to administration of cocaine or amphetamine to rats reduced the effects of these stimulant drugs, which normally cause a substantial increase in spontaneous locomotor activity. These results suggest that gabapentin may counteract some physiological actions of cocaine or other stimulants in animals.

These results would be consistent with behaviors associated with CNS depressant drugs.

d. Physical dependence study

(1) Source data was not available for review.

C. **Clinical pharmacology**

(1) Source data was not available for review.

D. **Clinical studies**

Sponsor's review of the adverse events related to gabapentin abuse observed in the reference listed drug's clinical studies is included in the Neurontin® (gabapentin) NDA supplement, NDA# 20-235, Item #3 - Summary. 2002. In Section 3.11.2.4 (Review of Adverse Event Terms from Clinical Trials with Possible Relevance to Abuse Potential), the summary states:

Current labeling for gabapentin includes infrequent reports (ie, labeled adverse events occurring in 1/100 to 1/1000 patients) of euphoria, doped-up sensation, and feeling high. Adverse event data from placebo-controlled clinical trials in patients with neuropathic pain were reviewed for terms that might be associated with abuse potential, such as euphoria, drug dependence, drug addiction and withdrawal. The only term identified was euphoria, which was reported by 2 patients in the gabapentin 3600 mg/day treatment group. Both events were mild in intensity. The overall incidence of euphoria within the neuropathic pain patient population was 0.2% for gabapentin-treated patients (2 of 820 patients) versus 0% (0 of 537 patients) for placebo-treated patients. Two clinical pharmacology studies in which doses ≥3600 mg/day of gabapentin were administered (Studies 945-190 and -057) were also reviewed for adverse event terms possibly associated with abuse potential.

Study 945-190, which is included in this NDA, was an open-label, multiple-dose, dose-proportionality study in which 14 healthy subjects each received escalating gabapentin doses of 1200, 2400, 3600, and 4800 mg/day. Euphoria was the only relevant term identified. Overall, 4 of the 14 subjects experienced euphoria, which was reported as mild to moderate in intensity. No subjects experienced euphoria at the 1200-

mg/day dose; 2 subjects at the 2400-mg/day dose; 4 subjects at the 3600-mg/day dose; and 1 subject at the 4800-mg/day dose.

Study 945-057, which was reported in the original gabapentin NDA, 20-235, was a double-blind, placebo-controlled, parallel group, single- and multiple-dose study in which 24 subjects received multiple doses of either gabapentin 1800, 2400, 3600, 4800 mg/day, or placebo for 2 weeks. The only term identified was feeling high. This event was reported by 1 subject in the 1800-mg/day treatment group and was mild in intensity. No other terms possibly associated with abuse potential were identified."

E. **Postmarketing experience of gabapentin**

Sponsor's historical review of the adverse events related to gabapentin abuse observed in the postmarketing period is provided in the Pfizer Neurontin® (gabapentin) NDA supplement, NDA# 20-235, Item #3 - Summary. 2002. In Section 3.11.2.5 (Review of Postmarketing Safety Databases), Sponsor provides the following:

As of December 2000, postmarketing exposure to gabapentin is estimated at greater than (b) (4) *patients. A review of the postmarketing safety databases was conducted for signals of potential drug abuse, drug addiction, and related clinical phenomena. These databases contain reports from health care professionals and consumers, adverse event registries, medical literature, and Phase 4 (postmarketing) clinical studies, regardless of causality. Database searches were performed for all reports entered from market launching 1993 through June 20, 2001, which included at least one of the following COSTART preferred adverse event terms: drug dependence, addiction, and euphoria. Sixty cases were identified and individually evaluated for appropriateness of inclusion in the review. These included 24 cases of drug dependence and/or addiction and 36 cases of euphoria. Based on a detailed medical review of the 24 cases of drug dependence, 16 cases were excluded from further review because the adverse event terminology did not reflect dependence (eg, mal-administration) or involved drug dependence exclusive to other specified or non-specified substances. Of the remaining 8 cases that coded to drug dependence and/or possible addiction, 5 cases described events potentially associated with gabapentin dependence or addiction; 2 cases described reports of drug-seeking behavior; and 1 case involved off-label use of gabapentin to relieve the effects of withdrawal from cocaine. These 8 cases comprised 0.09% (N=9038) of all adverse event cases entered into the gabapentin postmarketing database during the same time interval.*
Of the 36 reports of euphoria, 1 case in a recovering drug and alcohol abuser described self-administration of gabapentin for purposes of inducing euphoria. However, because of her fear of addiction, she voluntarily discontinued gabapentin and did so without difficulty. None of the reports of euphoria described drug addiction, dependence, drug

seeking behavior or continued gabapentin use in the setting of adverse medical consequences. A review of the postmarketing safety data for gabapentin did not indicate a signal of significant abuse potential.

F. Integrated Abuse Potential Assessment

1. Prior regulatory review from FDA Division of Drug Risk Evaluation

A review of gabapentin by Thambi (2004) from the FDA/CDER - Division of Drug Risk Evaluation is excerpted below:

> *"The summary had indicated that from dates December 30, 1993 (approval) thru July 29, 2004, 96 distinct AERS cases of relevant adverse events of gabapentin were identified: withdrawal (36), drug seeking behavior (22), euphoria (19), addiction (18), and abuse (1). The cases of withdrawal (either due to a decrease in dose or discontinuation of gabapentin) described many events that are already addressed in the Postmarketing section of the labeling; however, tremor and depression are not listed and may be considered for addition. In the cases of drug-seeking behavior and addiction, the reporters did not provide the motive for these behaviors to determine whether or not gabapentin was used because it was effective for the prescribed indication or because it was being abused (patients seeking euphoria). In the cases of euphoria, the contribution of concomitant medications labeled for euphoria or scheduled medications and patients with past histories of drug or alcohol abuse make an association between gabapentin and euphoria difficult to establish. There was one report of abuse reported by a physician who claimed the patient was a psychopath. The postmarketing cases contain limited information and lack evidence of abuse for euphoric purposes. In addition, gabapentin did not exhibit affinity to several receptor sites commonly associated with addiction/abuse. No recommendations for labeling changes regarding abuse liability can be made at this time."*

Dr. Thambi's survey of abuse-related information regarding gabapentin in 2004 could not identify sufficient non-clinical and clinical data to suggest changes to the abuse liability section of the product label.

2. Postmarketing Safety Update Reports of Horizant (Gabapentin enacarbil) (PSUR) (9 months)

a. Review of the Sponsor's postmarketing report data since the launch of Horizant (9 months, April 6, 2011) for use in restless leg syndrome show only few cases exhibiting abuse-related symptoms:

(1) euphoria-related terms

(i) abnormal dreams (3)

(ii) euphoric mood (2)

(iii) feeling abnormal (3)
(iv) feeling drunk: (1)
(v) dizziness (12)
(vi) hypomania (2)
(vii) thinking abnormal
(viii) hallucination (4)

(2) Dissociative/psychotic terms:
(i) Confusional state (2)

(3) Impaired attention, cognition, mood, and psychomotor events:
(i) Somnolence (2)
(ii) Hypersomnia (2)
(iii) Psychomotor hyperactivity (2)

3. **Regulatory and prescription comparisons of gabapentin to Scheduled drugs**

The following scheduled drugs are included as references for comparison, to include: pregabalin (Schedule V with similar activity to gabapentin), diazepam (Schedule IV and a representative benzodiazepine), alprazolam (Schedule IV and a representative benzodiazepine), and zolpidem (Schedule IV and a representative hypnotic agent for sleep) (see Table 1).

Table 1: Gabapentin Regulatory Comparisons to Scheduled Drugs

	DEA Schedule	1st Approval Year	Formulations	Risk Evaluation and Mitigation Strategy (REMS)	# of Prescriptions in 2010
Gabapentin	-	1993	capsule (oral); tablet (oral); solution (oral)	Med Guide only	(b) (4)
Pregabalin	V	2004	capsule (oral)	Med Guide only	
Diazepam	IV	<1982	capsule (oral); solution (oral); gel (rectal); solution (injectable); tablet (oral)	No	
Alprazolam	IV	<1982	tablet (oral)	No	
Zolpidem	IV	1992	spray (oral); tablet (oral); tablet (sublingual)	No	

4. **Drug Abuse Warning Network (DAWN) review of gabapentin**

Drug Abuse Warning Network (DAWN) data (Tables 2, 3, 4) provided by CDER/Office of Safety and Epidemiology show similar abuse values between non-scheduled gabapentin and scheduled pregabalin and similar abuse ratios (Tables 4, 5, 6). However, in each of these cases, unknown causality

relationships particularly with a high polypharmacy rate makes interpretation of the data difficult. Gabapentin has been prescribed for unapproved uses and is used also as adjuncts to other therapies for pain control.

Table 2: National Estimates of All Emergency Department Visits Reported in DAWN associated with Gabapentin, Pregabalin, Alprazolam, Diazepam, and Zolpidem Products, Years 2004-2009

Drugs	2004	2005	2006	2007	2008	2009
gabapentin	14,973	12,563	13,049	16,849	24,407	29,736
pregabalin	*	579	6,472	8,464	16,868	13,007
alprazolam	67,916	85,953	99,832	125,393	170,244	181,239
diazepam	25,523	28,443	30,819	37,015	44,440	42,676
zolpidem	22,307	26,552	31,925	40,067	55,328	61,771

* estimates not available
Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

Table 3: National Estimates of AllMA (all misuse and abuse) Emergency Department Visits Reported in DAWN associated with Gabapentin, Pregabalin, Alprazolam, Diazepam, and Zolpidem Products, Years 2004-2009

Drugs	2004	2005	2006	2007	2008	2009
gabapentin	7,832	6,346	6,435	6,532	10,074	13,533
pregabalin	*	*	2,668	2,335	6,518	3,924
alprazolam	56,655	70,023	78,129	97,546	132,462	140,657
diazepam	19,096	22,332	23,368	24,413	33,214	30,214
zolpidem	13,903	16,659	20,269	21,595	33,715	35,438

* estimates not available
Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

Table 4: Summary of the Proportion of National Estimates of AllMA Relative to All ED Visits in DAWN for Gabapentin, Pregabalin, Alprazolam, Diazepam, and Zolpidem Products (Years 2004-2009)

	2004	2005	2006	2007	2008	2009
gabapentin	52%	51%	49%	39%	41%	46%
pregabalin	*	*	41%	28%	39%	30%
alprazolam	83%	81%	78%	78%	78%	78%
diazepam	75%	79%	76%	66%	75%	71%
zolpidem	62%	63%	63%	54%	61%	57%

* estimates were not available

Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

To account for relative drug exposure, the abuse ratio is defined by using annual prescriptions and dose units by year:

Abuse Ratio = (b) (4)

(b) (4)

5. **AERS database review of gabapentin**

a. OSE / Pharmacovigilance group performed an AERS search of drug abuse, dependence, and withdrawal Standard MedDRA Query (SMQ) from the past five years to mid-2011 and identified 496 and 581 crude count reports associated with gabapentin and pregabalin, respectively (Table 7). Specifically to minimize other suspect drug effects and isolate the active's contributing role, cases that were only gabapentin (n=78) and only pregabalin (n=174) (and had no other concomitant drugs) were identified separately. Since a detailed review of individual cases was not performed, the report narratives may reveal additional cases with concomitant medications that have not been coded properly during data entry into AERS nor were cases specifically identified in multi-drug cases with gabapentin as the primary suspect drug.

Table 7: Number of AERS Cases of Drug Abuse, Dependence, and Withdrawal SMQ for Gabapentin and Pregabalin (Past 5 years to July 12, 2011.)

Suspect Drugs	2006	2007	2008	2009	2010	2011H	Total
Gabapentin only	9	17	9	5	20	18	**78**
Gaba + other drugs	85	106	73	58	86	88	**496**
Pregabalin only	22	17	18	6	74	37	**174**
Pregab + other drugs	68	75	88	53	189	108	**581**

In order to minimize the confounding influences of other medications, gabapentin-only AERS reported cases (N=78) were line-listed in this frequency count analysis. Since spontaneous cases have limitations with accuracy and coding methodologies and definitions have been modified over the years of recording, the following are preferred terms that have been reported at minimum 10 times in the AERS database (see Table 8). These spontaneous adverse event cases were reported in the context of (b) (4) prescriptions from 1969 to July 12, 2011.

Table 8: Terms Spontaneously Reported in At Minimum 10, Gabapentin-only AERS Reported Cases from 1969 to July 12, 2011

AERS Preferred Terms	Frequency*
Completed Suicide	10
Depression	13
Drug Abuse/Drug Abuser	27
Drug Dependence	44
Drug Ineffective	19
Drug Withdrawal Syndrome	38
Intentional Drug Misuse	14
Intentional Overdose	40
Medication Error	11
Suicidal Ideation	14
Suicidal Attempt	23

*Values represent number of mentions in the AERS database, multiple terms may be found in a single case

6. **Poison control center fatalities with gabapentin mentions**[7, 8, 9, 10, 11]

The information below represents a crude count of number of fatalities with active-ingredient mentions that were identified from the annual reports of the American Association of Poison Control Centers' (AAPCC) national poison control center databases. As noted in the 2010 publication, the information represents 61 regional poison centers serving the entire population of the 50

[7] Lai MW, Klein-Schwartz W, Rodgers GC, et al. 2005 Annual report of the American Association of Poison Control Centers' national poisoning and exposure database. Clin Tox. 2006. 44: 803-932.
[8] Bronstein AC, Spyker DA, Cantilena LR, et al. Clin Tox. 2007. 45: 815-917.
[9] Bronstein AC, Spyker DA, Cantilena LR, et al. Clin Tox. 2008. 46: 927-1057.
[10] Bronstein AC, Spyker DA, Cantilena LR, et al. Clin Tox. 2009. 47: 911-1084.
[11] Bronstein AC, Spyker DA, Cantilena LR, et al. Clin Tox. 2010. 48: 979-1178.

US states and related territories. Causality assessment is not always possible or provided; however, it does provide useful "signaling" of active ingredients that have been mentioned in fatalities. For the purpose of this analysis, the database was used due to its active-ingredient specific nature, continuity of reporting mechanisms for trending in comparing active ingredients that are DEA-scheduled drugs (except gabapentin). Fatality reports are based upon the best-efforts of each of the reporting poison control centers to conduct follow-up communications with the caller (see Table 9). Causality is difficult due to the commonness of polypharmacy abuse.

Table 9. Number of Fatalities with Mentions in Annual Poison Control report

Drug (Schedule)	2005	2006	2007	2008	2009
gabapentin (-)	11	20	21	12	19
pregabalin (C-V)	0	10	9	14	4
zolpidem (C-IV)	9	29	37	34	37
diazepam (C-IV)	24	27	36	49	32
alprazolam (C-IV)	64	69	73	125	89

This review showed that the majority of fatalities as reported by the poison control centers are polypharmacy, related to intentional suicides, and when overall suggested ranked causality was available, gabapentin was typically not ranked as the top suspect agents; opioids, antidepressants, and anxiolytics were the usual suspect agents. Gabapentin is known to be used on-label and off-label, including legitimate pain management therapies that use gabapentin as an adjunct to opioids for the treatment of chronic pain. Therefore, it is unclear whether the frequency of gabapentin has a direct relationship to fatalities because of reinforcing abuse-related effects or that these fatalities are formerly or were current chronic pain patients at the time of the event. Therefore, the sum of this data does not specifically help support gabapentin as a common drug of abuse.

7. **Literature review on gabapentin and abuse/dependence**

- (Hellwig et al., 2010) 53 F with hx of liver cirrhosis secondary to alcohol abuse, ascites, portal hypertension, varices, anemia, GERD, neuropathic pain, and depression, presents with coffee-ground emesis with 2-day hx of tarry stool and abdominal pain. Patient had multiple medications including citalopram, trazodone, and gabapentin 300mg in the morning and 100mg at night. Patient was admitted following varices banding procedure and **suffered withdrawal syndrome (restlessness, disorientation, confusion, agitation, and anxiety, light sensitivity, headaches, and nervousness) after gabapentin discontinuation**. Patient was reinitiated on gabapentin and patient's confusion and agitation

demonstrated swift improvement.[12] **This subject's behavior is consistent with gabapentin drug dependence**.

- (Kruszewski et al., 2009) 38 M pathologist suffered substance intoxication delirium and psychoactive substance dependence due to **self-administered high doses of gabapentin,** in combination with buspirone and buproprion, for depression and anxiety. Patient had history of alcohol dependence, driving under the influence violations, and work-related impairments. Patient was taking doses up to 4800 mg/day and subsequently monitored after controlled tapering. **31 weeks after discontinuation, patient reported cravings and "addiction" to gabapentin for treatment of anxiety and migraines**. Following relocation, the clinician reporting the case indicated the subject relapsed to alcohol and gabapentin use.[13] This subject's behavior would be **consistent with gabapentin drug abuse.**

- (Medtox Scientific, 2009) Female caller from a sober living home in CA indicated many residents in recovery from methamphetamine dependency were being prescribed gabapentin and concerned that gabapentin was itself an addictive drug and use could lead to diversion and abuse by other residents in her homes. Caller was assured by this drug testing company managing the hotline based upon anecdotal experience.[14] This subject's concern is associated **with potential addictive behavior of gabapentin** in its use as treatment for methamphetamine dependence.

- (Pittenger et al., 2007) (Case 1) 33 M w/history of hepatitis C, alcohol and other drug dependence w/concomitant use of cannabis taking 3600 mg/day of gabapentin, twice his prescribed dose, as a self-treatment for alcohol craving. **After chronic usage and early requests for refills, subject experienced withdrawal symptoms (confusion, diaphoresis, disorientation, and agitation) with full clinical improvement after restarting on gabapentin**. (Case 2) 63 M with hx of chronic back pain and multiple surgeries w/hx of inactive alcohol abuse was prescribed oxycodone and gabapentin. Pt was taking an average of 4900mg of gabapentin for past 11 days prior to presentation in ER for hallucinations and confusion. Pt was restarted on lower dose gabapentin with full improvement of mental status.[15] **These two subjects' behaviors are consistent with gabapentin drug abuse and drug dependence**.

- (Victorri-Vigneau et al., 2007) (France) 67 F with mood disorder and history of alcohol abuse leading to polyneuritis was on 550mg of

[12] Hellwig T, Hammerquist R, Termaat J. Withdrawal symptoms after gabapentin discontinuation. Am J Health Sys Pharm. 2010. 67(1): 910-2.
[13] Kruszewski SP, Paczynski RP, Kahn DA. Gabapentin-induced delirium and dependence. J Psych Pract. 2009. 15: 314-9.
[14] Medtox Scientific. DARS Hotline Call. Medtox Journal. St. Paul, MN. 2009. Oct.
[15] Pittenger C, Desan PH. Gabapentin abuse, and delirium tremens upon gabapentin withdrawal. J Clin Psych. 2007. 68:3.

naproxen, 100 mg of amitriptyline, and gabapentin daily. Patient developed a tolerance and self-escalated her dose up to 7200 mg per day. Patient subsequently exhibited prescriber-shopping behavior until she was hospitalized for withdrawal symptoms of trembling, sweating, excitation, pallor, and exophthalmia from lack of drug access. Patient was discharged with rehabilitated and discharged but demonstrated subsequent relapse of "abusive consumption" after a lower-dose prescription was provided.[16] **This subject's behavior is consistent with drug dependence**.

- (Del Paggio, 2005) Psychotropic medication abuse cases were reviewed and presented as part of a California correctional facility formulary review. In their summary review with clinicians and their formulary review, psychotropic medicines (including gabapentin, quetiapine, bupropion SR, trihexyphenidyl, and tricyclic antidepressants) were removed due to concerns of **burgeoning abuse problems**.[17] This institution's concern is about **gabapentin drug abuse**.

- (Reccoppa, 2004) Five male prisoners with histories of cocaine abuse or dependence and other psychiatric and medical disorders indicated they had opened capsules and **intra-nasally snorted gabapentin for feeling of altered mental state or "high".** Quantity of abused 300/400 mg gabapentin capsules was not noted.[18] These behaviors are consistent with abuse via insufflation.

- (Trinka et al., 2000) (Austria) (Case 1) 37 F with first generalized tonic-clonic seizure at age 37 who is fully functional and on 600 mg of gabapentin three times daily. After 5 days of treatment, patient **felt unusually well and euphoric, laughed inappropriately and felt full of energy.** Gabapentin was discontinued and symptoms resolved. (Case 2) 38 F was diagnosed with myocarditis of unknown etiology and treated with antipyretics and rest. Two weeks later, patient subsequently diagnosed with hemihypesthesia on left side with diagnosis of parainfectious encephalomyeltitis and treated with 300mg of gabapentin given three times daily. **Patient experienced one week later euphoria, inappropriate laughter, giggling, increased emergency and decreased need for sleep**. Speech was fast and difficult to interrupt. Gabapentin was continued for the neuropathic pain and symptoms resolved spontaneously after 2 weeks.[19] **These behaviors are consistent with gabapentin physical dependence and positive effects consistent with drugs of abuse.**

[16] Victorri-Vigneau C, Guerlais M, Jolliet P. Abuse, dependency and withdrawal with gabapentin: A first case report. Pharmacopsychiatry. 2006. 40:45-6.
[17] Del Paggio D. Psychotropic medication abuse in correctional facilities. Psychopharmacology Newsletter. 2005. June. 8(2).
[18] Reccoppa L, Malcolm R, Ware M. Gabapentin abuse in inmates with prior history of cocaine dependence. Am J Addictions. 2004. 13: 321-3.
[19] Trinka E, Niedermuller U, Thaler C, et al. Gabapentin-induced mood changes with hypomanic features in adults. Seizure. 2000. 505-8.

- (Markowitz, 1997) 41 F with history of crack cocaine and inappropriate use of husband's gabapentin, presented to inpatient facility for management of ongoing PTSD. Upon query, patient indicated she was **abusing gabapentin** since the last time she was using cocaine (about 3 months prior). Patient recalled a period of cocaine withdrawal (irritability, agitation, insomnia, depression, craving) shortly after discontinuation and noted husband's gabapentin helped with the craving. Physician reporter indicated ongoing evaluation of gabapentin for use in managing cocaine withdrawal.[20] **These behaviors are consistent with gabapentin drug abuse**.

8. **Internet-based abuse message boards comments on gabapentin**

a. Highlights from postings on Bluelight and Erowid, two-well known abuse-related internet-based message boards:

(1) Gabapentin is described with a highly varied range of effects including: euphoria, depression, sedation, anxiolysis, stimulation, dissociation, hallucinogenesis, somnogenesis, and elation.

(2) Wide range of drug dose levels for abuse are reported from total daily doses of 300mg to 9000 mg, and effects appear to be dose-dependent

(3) Combinations as part of polypharmacy and illicit substance abuse

(4) Recognition of pregabalin in multiple posts allude to possibly better desirable effects and greater potency

(5) Reference to difficulty in overdosing

(6) Routes of administration include: oral ingestion, insuffulation

(7) Used for mitigating withdrawal symptoms of other drugs, e.g. opioids, mood stabilizer

(8) Claims of potentiation with soda

(9) Variable experience even reported by the same person

[20] Markowitz JS, Finkenbine R, Myrick H, et al. Gabapentin abuse in a cocaine user: Implications for treatment? J Clin Psychopharm. 1997. 17(5): 423-4.

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/s/

STEPHEN W SUN
03/21/2012

MICHAEL KLEIN
03/21/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 8, 2012

TO: Sharon Turner-Rinehardt, Regulatory Project Manager
Robert Levin, M.D., Medical Officer
Frank Pucino, Pharm.D., Clinical Team Leader
Division of Anesthesia, Analgesia, and Addiction Products

FROM: Jean Mulinde, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader, Good Clinical Assessment Branch
Division of Good Clinical Practice Compliance
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Tejashri Purohit-Sheth, M.D.
Branch Chief, Good Clinical Practice Assessment Branch
Acting Division Director, Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 22399 S003

APPLICANT: Glaxo Group Limited d/b/a GlaxoSmithKline
DRUG: HORIZANT™ (gabapentin enacarbil) Extended-Release Tablets

NME: No
REVIEW PRIORITY: Standard Review

INDICATION: For the management of postherpetic neuralgia in adults.

CONSULTATION REQUEST DATE: November 18, 2011
DIVISION ACTION GOAL DATE: June 8, 2012
PDUFA DATE: June 9, 2012

I. BACKGROUND:

HORIZANT™ (gabapentin enacarbil) is a novel prodrug of gabapentin designed to provide dose-proportional and sustained exposure of gabapentin. It is converted to gabapentin upon absorption from the intestinal lumen. The sustained exposures of gabapentin achieved after dosing with gabapentin enacarbil extended-release tablets allow for less frequent dosing intervals versus gabapentin. Gabapentin enacarbil (GEn) was previously approved by the FDA for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) on 06 April 2011. Gabapentin is thought to bind to the α2δ subunit of a voltage-gated calcium channel which is located on the presynaptic terminals of αδ and C-fibers projecting to the dorsal horn and throughout the central nervous system (CNS). Although the exact mechanism of pain relief is not known, it is speculated that this binding reduces calcium influx during depolarization, with an ensuing decrease in pain generating neurotransmitters such as glutamate and substance P. The Applicant proposes GEn also has efficacy for the treatment of postherpetic neuralgia based on results of animal models of analgesia, for which gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). Based on evaluation of the risk versus benefit profile of GEn observed in clinical studies, the Applicant proposes that the recommended dose for use in the management of PHN in adults is GEn 1200 mg/day (600 mg BID).

The most commonly observed adverse events (AEs) associated with previously approved formulations of gabapentin include dizziness, somnolence and peripheral edema. The AEs that have most frequently led to patient discontinuation of treatment with gabapentin include dizziness, somnolence and nausea. The AE profile of GEn is consistent with that of gabapentin with the most frequently reported AEs in clinical studies being peripheral edema, somnolence, and dizziness. Additional AEs that have been reported more frequently in GEn treated subjects than in placebo subjects in clinical studies include: confusional state, depression, dry mouth, flatulence, increased appetite, irritability and vertigo.

Based, in part, on the outcome of one Phase IIb clinical study (PXN 110748), GSK is seeking approval to market GEn for the treatment of adults with post herpetic neuralgia; therefore, the protocol inspected for this application was:

> Protocol PXN110748, entitled "An Efficacy and Safety Study of Gabapentin Enacarbil (GEn) (GSK1838262/XP13512) Compared with a Concurrent Placebo Control in Subjects with Neuropathic Pain Associated with Post-Herpetic Neuralgia (PHN)"
>
> Study PXN110748 was a Phase IIb randomized, double-blind, multicenter, parallel-group, placebo-controlled study to evaluate the efficacy and safety of three maintenance doses of GEn (GSK1838262, XP13512) to treat peripheral neuropathic pain associated with PHN. The total duration of the study was 22-weeks, including six treatment periods (a screening period, a one-week baseline period, a one-week up titration period, a 12-week maintenance treatment phase, a one-week down-titration period and a follow up post-treatment phase of up to 16 days). Once determined to be eligible during the baseline period, subjects were randomized to treatment in a 1:1:1:1 ratio: GEn 1200 mg/day, GEn 2400 mg/day, GEn

3600 mg/day, or matching placebo. The study was conducted at 72 clinical investigator sites in the United States and Canada. A total of 376 subjects were randomized into the trial. Subjects were enrolled in the study from February 6, 2008 through July 29, 2009 (Date of final study report: March 8, 2010).

GSK conducted site monitoring activities. [redacted] monitored e-diary activities [redacted] Activities performed using the [redacted] included data entry, modification, review, and validation. An electronic audit trail of all changes made to the eCRF was kept within the [redacted]. The principal investigator electronically signed and dated each [redacted] casebook attesting to his/her responsibility for the quality of all data included therein, and that the data represented a complete and accurate record of each subject's participation in the study. Subjects' responses to health outcome questionnaires/daily diaries were collected directly from the subject via a secure, standardized and validated electronic data capture system [redacted] Each record collected via this tool carried a date-time stamp. Encrypted data was transmitted from the handheld device to a firewall-protected website, and then via an application server to GSK. While held on [redacted] website, any changes to the data were recorded on an electronic audit trail. This audit trail identified the user making the change by userid, and date and time of change. Subject specific PDFs (portable document format) were created and sent to the appropriate site as well as archived centrally at GSK. According to the NDA submission, at the end of the study once all data queries were resolved, a CD-ROM containing eCRF PDFs was returned to investigators (the PDF contains all of the subject's eCRF data, the data queries, and a copy of the Patient Reported Outcome data from the subject's e-diary).

The primary efficacy endpoint for this study was the change from baseline to end of treatment with respect to the mean 24-hour average pain intensity score based on the 11-point PI-NRS. The mean score was the calculated mean of the daily 24-hour average pain scores for each subject during the last 7 days of the Maintenance Treatment Period. Safety measurements included assessment of adverse events, clinical laboratory measurements, 12-lead electrocardiograms (ECGs), vital signs, and physical examinations.

The clinical investigator sites chosen for inspection were amongst the highest enrolling domestic and foreign centers.

II. RESULTS (By Site)

Name of CI	Protocol # Site# Subject#	Inspection Date	Final Classification
Michael C. DeSantis, MD Clinical Trials of America, Inc 1730 N. Center Street Hickory, NC 28601	Protocol: PXN 110748 Site #051926 Enrolled: 14	January 3-5, 2012	VAI

Name of CI	Protocol # Site# Subject#	Inspection Date	Final Classification
Francois Blouin, MD Pro-Recherche Polyclinique des Ponts 1100 Boul. De La Rive-Sud, Bureau 120 Saint-Romuald, QC G6W 5M6 Canada	Protocol: PXN 110748 Site #048870 Enrolled: 20	February 13-17, 2012	Pending (Preliminary Classification VAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI* = Significant deviations from regulations. Data unreliable Study C119.
Pending = Preliminary classification based on information in 483 and preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Michael C. DeSantis, MD**
   Clinical Trials of America, Inc
   1730 N. Center Street
   Hickory, NC 28601
   Site #051926

   a) What was inspected:
   For Study PXN110748, at this site, 27 subjects were screened, 14 subjects were enrolled (randomized), and 9 subjects completed the study. All fourteen randomized subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated clinical laboratory report documentation, protocol deviation reports, concomitant medication usage, test article accountability, and IRB approvals and correspondence. There were no limitations to the inspection.

   b) General observations/commentary:
   Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the sponsor to the agency in NDA 22399 S003 were compared. Generally, the investigator's execution of the protocol was found to be adequate. Of note, subjects in this study answered a series of questions on hand held electronic diaries (known as (b) (4)) to record information such as time of drug administration, daily rescue medication use, pain intensity scores (PI-NRS), sleep interference, total sleep time, and sleep awakenings. These data were then

transferred directly, via modem, to (b) (4). The site was able to access subjects' eDairy information via a web based (b) (4) to monitor the frequency that subjects were entering data into eDairies. The average PI-NRS scores could also be viewed via (b) (4) by site personnel and were used to determine whether a subject met inclusion criteria, which required a baseline 24-hour average PI-NRS score ≥ 4.0. Records at the site documented that site staff did view (b) (4) during the conduct of the study and used viewed data to determine subject eligibility. Individual (b) (4) values/entries, however, could not be seen by the study site. In addition, according to the ORA investigator conducting the inspection, the archival CD returned to the site at the conclusion of the study did not contain subjects' individual PI-NRS entries; therefore, during this inspection subjects' entries for individual PI-NRS scores could not be verified.

While a Form FDA 483 was not issued to the Clinical Investigator (CI), the ORA field investigator noted in the EIR, and provided evidentiary support, that the CI enrolled/randomized two subjects that should have been excluded from the protocol based on screening creatinine clearance values. According to the protocol, subjects with CrCl < 60 mL/min were to be excluded; however, Subject #7753 (randomized to 1200 mg group) with a screening CrCl=52 mL/min, and Subject #7755 (randomized to placebo group) with a screening CrCl=39 mL/min were randomized and received study therapy. Randomizations of these subjects in error were reported to the sponsor as protocol deviations, but not until approximately one year after randomization and treatment had occurred. Given that gabapentin is renally excreted, and the current HORIZANT™ label requires dosage reduction for patients with CrCl<60, the CIs failure to follow the protocol by enrolling these subjects placed them at potentially increased risk. (Of note, Subject #7753 withdrew from the study on Day 8 with complaints of intolerable fatigue and numbness.) OSI's final classification for this inspection, therefore, will be VAI due the CI's failure to follow the protocol.

c) **Assessment of data integrity:**
Not withstanding the observations noted above (i.e. that individual PI-NRS scores could not be verified at the site and the enrollment of two subjects that should have been excluded due to screening CrCl values), the data provided by Dr. DeSantis's site for Study PXN110748 that were submitted to the Agency in support of NDA 22399 S003 appear to be reliable and acceptable for use in support to the pending application.

2. **Francois Blouin, MD**
Pro-Recherche Polyclinique des Ponts
1100 Boul. De La Rive-Sud, Bureau 120
Saint-Romuald, QC G6W 5M6
Canada
Site #048870

a) What was inspected:

For Study PXN110748, at this site, 53 subjects were screened, 19 subjects were enrolled (randomized), and 10 subjects completed the study. All randomized subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and CRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated test article accountability, IRB approvals, monitoring visit logs, and monitoring correspondence to the site. There were no limitations to the inspection.

b) General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the sponsor to the agency in NDA 22399 S003 were compared and verified. Generally, the investigator's execution of the protocol was found to be adequate; however, a Form FDA 483 was issued to the CI with the following observations related to conduct of the study:

i. Failure to ensure the study was conducted in accordance with the investigational plan and protocol. Specifically for:
   - The enrollment/randomization of one subject that should have been excluded due to having a CrCl < 60 mL/min, which was contrary to protocol eligibility criteria. This subject was removed from the study, however, prior to receipt of any study drug.
   - Not dispensing study medication kits according to the schedule specified in the protocol. Rather than dispensing 5 MediSets at the Treatement Up-Titration Visit, as specified by the protocol, the site dispensed the kits over multiple visits.

<u>OSI Reviewer Comment:</u> Based on preliminary communications with the field, neither of these issues resulted in harm to subjects or ultimately error in the correct study drug being received by subjects. The site's failure to follow the protocol specified study medication dispensing schedule did result in some deviations in appropriate record keeping practices because study records were not designed to capture the dispensing of medications at the additional time points that were used by the site.

c) Assessment of data integrity:

Not withstanding the observations noted above (i.e. that individual PI-NRS scores could not be verified, and the Form FDA 483 observations noted at this site), the data provided by Dr. Blouin's site for Studies PXN110748 that were submitted to the Agency in support of NDA 22399 S003 appear to be reliable and acceptable for use in support to the pending application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review on preliminary summary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon final review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of inspectional findings for clinical investigators Dr. DeSantis and Dr. Blouin, the data submitted by these sites for Study PXN110748 appear reliable in support of NDA 22399 S003.

The final classification for the inspection of Dr. DeSantis is Voluntary Action Indicated (VAI) and the preliminary classification for the inspection of Dr. Blouin is also VAI, in each case, primarily for their failure to follow the investigational plan by enrollment of subjects that should have been excluded from the study due to the subjects' screening creatinine clearance values of < 60 mL/min.

Note: All observations noted above related to the inspection of Dr. Blouin are based on the Form FDA 483, if issued and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR for this inspection.

{See appended electronic signature page}

Jean Mulinde, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief, Good Clinical Practice Assessment Branch
Acting Division Director, Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

JEAN M MULINDE
03/08/2012

SUSAN LEIBENHAUT
03/08/2012

TEJASHRI S PUROHIT-SHETH
03/09/2012

DSI CONSULT: Request for Clinical Inspections

Date: November 18, 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Jean Mulinde, MD
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Robert Levin, MD, Medical Officer*
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: *Sharon Turner-Rinehardt, Senior Regulatory Health Project Manager*
DAAAP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22399/S-003
Applicant/ Applicant contact information (to include phone/email):GlaxoSmithKline
Drug Proprietary Name: Horizant
NME or Original BLA (Yes/No):No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication: Management of postherpetic neuralgia in adults

PDUFA: June 9, 2012
Action Goal Date: June 8, 2012
Inspection Summary Goal Date: April 16, 2012

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

GlaxoSmithKline has submitted this sNDA seeking approval of gabapentin enacarbil extended-release tablets for the management of post herpetic neuralgia (PHN) in adults. To support the efficacy for this 505(b)(2) application, the applicant has submitted a single Phase 2 trial, PXN110748 entitled, "An efficacy and safety study of gabapentin enacarbil (GEn) (GSK1838262/XP13512) compared with a concurrent placebo control in subjects with neuropathic pain associated with post-herpetic neuralgia (PHN)."

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #048870 Francois Blouin, MD Pro-Recherche Polyclinique des Ponts 1100 Boul. De La Rive-Sud, Bureau 120 Saint-Romuald, QC G6W 5M6, Canada FAX: 418-839-8003 Telephone: 418-839-8572	PXN 110748	20	Management of postherpetic neuralgia (PHN) in adults
Site #051926 Michael C. DeSantis, MD Clinical Trials of America, Inc 1730 N. Center Street Hickory, NC 28601 Telephone: 828-322-3222	PXN 110748	14	Management of postherpetic neuralgia (PHN) in adults

III. Site Selection/Rationale

The two sites with highest enrollment were chosen.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

N/A

Should you require any additional information, please contact *Sharon Turner-Rinehardt* at *301-796-2254 or Robert Levin* at 301-796-1963.

Concurrence: (as needed)

Frank Pucino Medical Team Leader
Robert Levin Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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

/s/

SHARON M TURNER RINEHARDT
11/18/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-399/S-003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEBARMENT CERTIFICATION

GlaxoSmithKline certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (Supplemental NDA 22399 Horizant™(gabapentin enacarbil) Extended-Release Tablets in the management of Postherpetic Neuralgia).

Craig Wozniak

May 2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022399 BLA #	NDA Supplement # 003 BLA Supplement #	If NDA, Efficacy Supplement Type: SE1
Proprietary Name: Horizant Established/Proper Name: Gabapentin Enacarbil Extended Release Dosage Form: Tablets		Applicant: GlaxoSmithKline Agent for Applicant (if applicable):
RPM: Sharon Turner-Rinehardt		Division: DAAAP

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☒ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 020235 Neurontin

Provide a brief explanation of how this product is different from the listed drug.

This supplement provides for a change in dosage form from capsules to tablets. Also, a change in formulation to extended-release as well as change in dosing regimen from 600 mg TID to 600 mg BID.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is June 9, 2012	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☒ Verified

Version: 1/27/12

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☒ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☒ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☒ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	Included, June 7, 2012
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) June 6, 2012
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	June 5, 2012
• Original applicant-proposed labeling	August 9, 2011
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	June 5, 2012
• Original applicant-proposed labeling	August 9, 2011
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	N/A
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM June 4, 2012 ☐ DMEPA ☒ DMPP/PLT (DRISK) April 23, 2012 ☒ ODPD (DDMAC) May 7, 2012 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	May 21, 2012
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) May 14, 2012
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) June 5, 2012
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: orphan drug designation • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	August 23, October 21 and December 8, 2011
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg March 17, 2011
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None June 6, 2012
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None May 19, 2012
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	N/A
• Clinical review(s) *(indicate date for each review)*	May 5, 2012/Filing review- October 7, 2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical Review- May 5, 2012
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not applicable March 21, 2012
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested March 6 and 9, and May 21,2012
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None May 9, 2012/Filing review - October 7 2011
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None May 3 and May 17, 2012/Filing review October 3, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None May 4, 2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None January 27 and June 1, 2012
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

Version: 1/27/12

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	June 1, 2012 (included in CMC review)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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/s/

SHARON M TURNER RINEHARDT
06/07/2012

EXCLUSIVITY SUMMARY

NDA # 022399 SUPPL # 003 HFD # 170

Trade Name Horizant

Generic Name Gabapentin Enacarbil Extended-Release Tablets

Applicant Name GlaxoSmithKline

Approval Date, If Known June 6, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020235 Neurontin

NDA# 020882, Neurontin Oral Tablets

NDA# 021129, Neurontin Oral Solution

NDA# 022544, Gralise Oral Tablets

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application

or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

There was one “new” clinical investigations submitted by the Applicant that was essential to the approval of this product (the investigation is also listed in 2(c)):

Protocol Number PXN110748: An efficacy and safety study of gabapentin enacarbil (GSK1838262/XP13512) compared with a concurrent placebo control in subjects with neuropathic pain associated with postherpetic neuralgia

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 068341	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
Investigation #2	!
	!

YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Sharon Turner-Rinehardt
Title: Senior Regulatory Health Project Manager
Date: June 6, 2012

Name of Office/Division Director signing form: Rigoberto Roca
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

SHARON M TURNER RINEHARDT
06/06/2012

RIGOBERTO A ROCA
06/06/2012

From:	Turner-Rinehardt, Sharon
To:	"Eric Benson"
Subject:	sNDA 22399/S-3 Horizant for PHN: Information Request
Date:	Thursday, December 08, 2011 2:22:00 PM
Importance:	High

Dear Eric,

You submitted the supplemental NDA via a 505(b)(2) pathway on August 9, 2011. You relied on literature information for the pharmacokinetics of 900 mg/day Neurontin and claimed that steady state exposure of gabapentin at the recommended GEn dose of 1200 mg/day is predicted to be approximately 34% higher than that at the 900 mg/day dose for Neurontin.

You stated that pharmacokinetics information for the 900 mg/day Neurontin was obtained from the literature entitled “Clinical Pharmacokinetics of Gabapentin” in your sNDA submission. During the review process, we found this publication is a review paper and the author cited an abstract published in Eur J Clin Pharmacol in 1989 regarding the pharmacokinetics data for the 900 mg/day Neurontin. However, the systemic exposure information could not be found in that abstract. Therefore, you are required to provide more detailed data (e.g. detailed PK parameters for Neurontin) for the cited study. Also, if necessary, you should provide appropriate information to demonstrate that you have the right to use these data.

We ask that you provide the requested information by December 28, 2011. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Addiction Products
Phone: (301) 796-2254
Fax: (301) 796-9713
Email: sharon.turner-rinehardt@fda hhs.gov

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/s/

SHARON M TURNER RINEHARDT
12/14/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022399/S-003

FILING COMMUNICATION

GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Eric Benson, Senior Director
Global Regulatory Affairs

Dear Mr. Benson:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 9, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Horizant (gabapentin enacarbil).

This supplemental application proposes a new indication for the management of postherpetic neuralgia.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is June 9, 2012.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 12, 2012.

During our filing review of your supplemental application, we identified the following potential review issue:

Submit the assay validation reports and within-in study bioanalytical reports for Studies XP009, PXN110748, and 110527. If you have submitted these reports, provide the location in the supplemental NDA.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. We note that a (b) (4)

2. Provide the narrative of the clinical study report (CSR) submitted in your August 4, 2011, Periodic Safety Report (it is line-listed as euphoric mood, one of the several non-serious AEs) and any other similar individual clinical safety report (ICSR) with narratives related to misuse and abuse since the launch.

3. Provide an evaluation of the poison control data for gabapentin-related abuse cases.

4. Provide an updated (literature or internal studies) summary of recent gabapentin abuse potential studies in animals experience.

5. Provide any information on the binding profile of gabapentin enacarbil (GEn) on cannabinoid receptors.

6. Propose labeling language to provide (b) (4)

7. Provide a summary of dependence (withdrawal) assessment based on the GEn clinical experience considering its chronic use.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Sharon Turner-Rinehardt, Senior Regulatory Health Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BOB A RAPPAPORT
10/21/2011

Screening of New NDA
Division of Biometrics II

Date: 10/6/11

NDA #: 22-399 S003

Priority Classification: S

Trade Name: Horizant Extended Release Tablets

Applicant: GlaxoSmithKline

Generic Name: Gabapentin enacarbil

Date of Submission: 8/9/11

Indication: Post-herpetic Neuralgia (PHN)

No. of Controlled Studies: 1

User Fee Goal Date: 6/9/12

Date of 45-Day Meeting: 9/22/11

Medical Officer: Robert A. Levin, M.D.

Project Manager: Sharon Turner-Rinehardt

Screened by: Kate Meaker, M.S.

Statistical sections: Sections 2.5, 2.7, and 5.3.5

Anticipated Review Completion Date: 3/31/12

Comments:

1. Fileable for statistics review.

CHECKLIST

Item	**Check (NA if not applicable)**
Index sufficient to locate necessary reports, tables, etc.	**Yes**
Original protocols & subsequent amendments available in the NDA	**Yes**
Designs utilized appropriate for the indications requested	**Yes**
Endpoints and methods of analysis spelled out in the protocols	**Yes**
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	**Not applicable**
Appropriate references included for novel statistical methodology (if present)	**Not applicable**
Data from primary studies provided in SAS .xpt files with documentation	**Yes**
Intent-to-treat analysis	**Yes**
Effects of dropouts on primary analyses investigated	**Yes (LOCF and BOCF imputations provided as discussed at pre-NDA meeting)**
Safety and efficacy for gender, racial, and geriatric subgroups investigated	**Yes**

BRIEF SUMMARY OF CONTROLLED CLINICAL TRIAL

Study Number (Dates Conducted)	**Number of Centers (Locations)**	**Total Sample Size**	**Design**	**Duration of Treatment**
PXN 110748 (2/08 – 7/09)	72 centers (US, Canada)	PBO: 95; GEn 1200mg: 107 GEn 2400mg: 84 GEn 3600mg:90	Randomized, Double-blind, Placebo-control Parallel arm	14 weeks total: 1 wk titration 12 wk maintenance 1 wk taper

_____

Katherine B. Meaker
Mathematical Statistician

Concur: Dionne Price Ph.D.
Team Leader

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/s/

KATHERINE B MEAKER
10/07/2011

DIONNE L PRICE
10/11/2011
Concur

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 22399 **Applicant:** GlaxoSmithKline **Stamp Date:** August 9, 2011

Drug Name: Horizant (gabapentin enacarbil) Extended-Release Tablets **NDA/BLA Type:** Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			Module 1 contains annotated, clean and proposed label
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Module 5
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Module 5
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 2 Section 5
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2) Reference Drug: Neurontin (gabapentin) NDA 020235
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: PXN110748 Study Title: *An efficacy and safety study of gabapentin enacarbil (GEn) (GSK1838262/XP13512) compared with a concurrent placebo control in subjects with neuropathic pain associated with post-herpetic neuralgia (PHN)* Sample Size: 376 Subjects Arms: PBO Location in submission: 1200 mg/day Module 5 2400 mg/day 3600 mg/day	X			This study designed to assess different doses may not have assessed a low enough dose. The lowest dose studied 1200 mg/day appears as effective as the higher doses studied In the RLS NDA the lowest dose studied (600mg/day) was

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					approved but a PMC was made to study lower doses.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: PXN110748 Indication: Neuropathic pain associated with post-herpetic neuralgia	X			The Division stated that as a b2 application for a prodrug, only one additional study would be needed if the sponsor was able to reference the studies from the listed drug (gabapentin) and demonstrate that most of the active drug in the circulation was gabapentin and not the prodrug.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Principal efficacy study is a randomized, double-blind, placebo-controlled
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. The primary endpoint used is acceptable to the Division.	X			Primary endpoint was change from baseline to end of maintenance treatment with respect to the mean 24-hour average pain intensity score based on an 11-point scale.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Unable to locate a statement in the electronic submission regarding the rationale for assuming the applicability of foreign data to the US population. Principal study 110748 was conducted in the US and Canada with Canada randomizing 49 of the 376 subjects (13%). Supporting Study XP009 was conducted solely in the US and Study 110527 was conducted primarily in the US with Germany randomizing 17 of 96 subjects (18%)
SAFETY					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)? Note: The thorough QT study submitted in the RLS NDA was not considered adequate since the moxifloxacin response failed to meet the Agency's criteria for assay sensitivity. The sponsor as a PMC will repeat the thorough QT study.		X		The Division said that the thorough QT study submitted in RLS NDA 022399 would support the filing of the PHN sNDA. However, whether the QT study provides sufficient information to proceed with the approval of the PHN sNDA will depend on the totality of the data
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious? 417 subjects in Phase 2 PHN studies received at least 1 dose of GEn with 206 subjects receiving ≥1200 mg for >90 days. For all indications a total of 2756 subjects were exposed to at least one dose. In the RLS Studies 334 subjects were exposed to 1200 mg/day or greater for one year	X			The Division agreed in the Pre-NDA meeting that exposure appeared to be sufficient based on the Agency's previous findings of safety for gabapentin in the management of PHN and extensive exposure to GEn in multiple indications
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data				Preclinical study

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	requested by the Division during pre-submission discussions? The sponsor submitted to IND 63341 (April 26, 2011) a rationale for not needing the study. The sponsor concluded that the risk for abuse potential in NDA 022399 (RLS) is negligible. They noted that GEn was approved without any PMR for preclinical or clinical abuse potential studies. They also note that gabapentin, the parent molecule of GEn, is not a controlled substance despite extensive clinical use over 18 years.		X		requested in Pre-NDA meeting to evaluate self-administration, drug discrimination, and dependence not done CSS felt this is not a filing issue, but will defer their decision regarding the need for a study until the time of the review
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Pediatric assessment not required for orphan-drug designation and the Division stated in the Pre-NDA meeting that a full waiver for pediatric assessment would be granted
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?		X		See response to Question 26
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		See response to Question 17
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			PHN CRFs in primary-rls folder subfolder 5354
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial				

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?	X			Form 3454 included
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Robert A. Perry, MD — September 13, 2011

Reviewing Medical Officer — Date

Paul Bamford — 09-16-11

Clinical Team Leader — Date

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/s/

ROBERT A LEVIN
10/07/2011

FRANK PUCINO
10/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE
Danyal Chaudhry, PM, OSE

FROM: Sharon Turner-Rinehardt, RPM (Robert Levin, MO)
Division of Anesthesia, Analgesia and Addiction Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 20, 2011		22399/S-003	New sNDA	August 9, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Horizant (gabapentin enacarbil ER tablets)	S		April 2, 2012

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*: PI and REMS

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Submitted for your review are the package insert and REMS for this supplemental NDA. A link to the entire submission is provided below and in the calendar notices for the meetings for your reference. If you have any questions, please contact Sharon Turner-Rinehardt, X6-2254.**

Submission link: EDR Link: \\CDSESUB1\EVSPROD\NDA022399\022399.enx (refer to amendment 56)

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Sharon Turner-Rinehardt/092011	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

SHARON M TURNER RINEHARDT
09/20/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
CSS Sandra Saltz	Sharon Turner-Rinehardt, RPM/DAAAP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 31, 2011		22399/s-3	Efficacy Supplement	August 9, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Horizant (gabapentin enacarbil)	S		May 5, 2012

NAME OF FIRM: GSK

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This consult is for the review of supplemental NDA 22399/s-3, Horizant, for post-herpetic neuralgia (PHN) submitted by GSK. The link to the supplement (sequence 56) is provided in this consult.

EDR Location: \\CDSESUB1\EVSPROD\NDA022399\022399.enx

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Sharon Turner-Rinehardt	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

SHARON M TURNER RINEHARDT
08/31/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022399/S-003

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Eric Benson, Senior Director
Global Regulatory Affairs

Dear Mr. Benson:

We have received your August 9, 2011, Supplemental New Drug Application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 022399

SUPPLEMENT NUMBER: 003

PRODUCT NAME: Horizant (gabapentin enacarbil)

DATE OF SUBMISSION: August 9, 2011

DATE OF RECEIPT: August 9, 2011

This supplemental application proposes the addition of a new indication of postherpetic neuralgia for gabapentin enacarbil extended release tablets.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 8, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-2254

Sincerely,

{See appended electronic signature page}

Sharon Turner-Rinehardt
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON M TURNER RINEHARDT
08/23/2011