

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**022399Orig1s005**

*Trade Name:* HORIZANT

*Generic or Proper Name:* gabapentin enacarbil extended-release tablets

*Sponsor:* Glaxo Group Limited d/b/a GlaxoSmithKline

*Approval Date:* March 27, 2013

This supplement provides for:

- Final study reports for Study RXP114111 (PMR 1588-7) and Study RXP115720 (PMR 1588-10).
- Revisions to the package insert based on the results of the studies referenced above.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 022399Orig1s005

### CONTENTS

#### Reviews / Information Included in this NDA Review.

<b>Approval Letter</b>	<b>X</b>
<b>Other Action Letters</b>	
<b>Labeling</b>	<b>X</b>
<b>REMS</b>	
<b>Summary Review</b>	<b>X</b>
<b>Officer/Employee List</b>	
<b>Office Director Memo</b>	
<b>Cross Discipline Team Leader Review</b>	<b>X</b>
<b>Medical Review(s)</b>	<b>X</b>
<b>Chemistry Review(s)</b>	
<b>Environmental Assessment</b>	
<b>Pharmacology Review(s)</b>	
<b>Statistical Review(s)</b>	<b>X</b>
<b>Microbiology / Virology Review(s)</b>	
<b>Clinical Pharmacology/Biopharmaceutics Review(s)</b>	<b>X</b>
<b>Other Reviews</b>	
<b>Risk Assessment and Risk Mitigation Review(s)</b>	
<b>Proprietary Name Review(s)</b>	
<b>Administrative/Correspondence Document(s)</b>	<b>X</b>

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022399Orig1s005**

**APPROVAL LETTER**



NDA 022399/S-005

**SUPPLEMENT APPROVAL**

**FULFILLMENT OF POSTMARKETING  
REQUIREMENTS**

Glaxo Group Limited  
d/b/a GlaxoSmithKline  
Attention: Debra H. Lake, M.S.  
Director, Regulatory Affairs  
PO Box 13398, Five Moore Drive  
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your Supplemental New Drug Application (sNDA) received February 29, 2012, 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 April 23, 2012, June 22, 2012, July 6, 2012, November 9, 2012, January 4, 2013, January 9, 2013, February 5, 2013, and February 15, 2013.

This "Prior Approval" supplement provides for:

- Final study reports for Study RXP114111 (PMR 1588-7) and Study RXP115720 (PMR 1588-10).
- Revisions to the package insert based on the results of the studies referenced above.

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/DrugsGuidanceComplianceRegulatoryInformation/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).

### **FULFILLMENT OF POSTMARKETING REQUIREMENTS**

We have received your submission dated February 29, 2012, containing the final reports for the following postmarketing requirements listed in the April 6, 2011 approval letter.

- 1588-7** A simulated driving trial in healthy adult subjects treated with 600 mg gabapentin enacarbil that includes active comparator and placebo arms.
- 1588-10** A clinical drug-drug interaction trial to evaluate the pharmacokinetic and the pharmacodynamic interaction between gabapentin enacarbil and morphine.

We have reviewed your submission and conclude that the above requirements were fulfilled.

### **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>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

### **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 Nicole L. Bradley, PharmD, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

*{See appended electronic signature page}*

Russell G. Katz, MD  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
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/  
-----

RUSSELL G KATZ  
03/27/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022399Orig1s005**

**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, Discontinuation of HORIZANT (5.6)	06/2012
Warnings and Precautions, Effects on Driving (5.1)	03/2013

**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](http://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: 03/2013

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**1 INDICATIONS AND USAGE**

- 1.1 Treatment of Restless Legs Syndrome
- 1.2 Management of Postherpetic Neuralgia

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Restless Legs Syndrome
- 2.2 Postherpetic Neuralgia
- 2.3 Renal Impairment

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Effects on Driving
- 5.2 Somnolence/Sedation and Dizziness
- 5.3 Lack of Interchangeability With Gabapentin
- 5.4 Suicidal Behavior and Ideation
- 5.5 Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity
- 5.6 Discontinuation of HORIZANT
- 5.7 Tumorigenic Potential

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experience
- 6.2 Adverse Events Associated With Gabapentin

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment

**9 DRUG ABUSE AND DEPENDENCE**

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

**10 OVERDOSAGE**

- 10.1 Human Overdose Experience
- 10.2 Overdosage Management

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**14 CLINICAL STUDIES**

- 14.1 Restless Legs Syndrome (RLS) 12-Week Pivotal Studies
- 14.2 Postherpetic Neuralgia (PHN) 12-Week Study
- 14.3 Effects on Driving

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

- 17.1 Effects on Driving
- 17.2 Somnolence/Sedation and Dizziness
- 17.3 Suicidal Behavior and Ideation
- 17.4 Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity
- 17.5 Lack of Interchangeability With Gabapentin
- 17.6 Dosing Instructions
- 17.7 Alcohol

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

1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 **1.1 Treatment of Restless Legs Syndrome**

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

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

8 **1.2 Management of Postherpetic Neuralgia**

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

11 **2 DOSAGE AND ADMINISTRATION**

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

13 Tablets should be taken with food.

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

16 **2.1 Restless Legs Syndrome**

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

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

22 **2.2 Postherpetic Neuralgia**

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

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

30 **2.3 Renal Impairment**

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

34

35 **Table 1. Dosage of HORIZANT for Patients With Restless Legs Syndrome in Accordance**  
 36 **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

37  
 38 **Table 2. Dosage of HORIZANT for Patients With Postherpetic Neuralgia in Accordance**  
 39 **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 <sup>a</sup>	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 <sup>a</sup>	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 <sup>a</sup>	None
<15 on hemodialysis	None	300 mg following every dialysis. Increase to 600 mg following every dialysis if needed <sup>a</sup>	None

40 <sup>a</sup> Based on tolerability and efficacy

41  
 42 In patients with stable renal function, CrCl can be estimated using the equation of  
 43 Cockcroft and Gault:

44 for males:  $CrCl = (140 - \text{age})(\text{weight}) / [(72)(SCr)]$

45 for females:  $CrCl = (0.85)(140 - \text{age})(\text{weight}) / [(72)(SCr)]$

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

### 47 **3 DOSAGE FORMS AND STRENGTHS**

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

### 51 **4 CONTRAINDICATIONS**

52 None.

### 53 **5 WARNINGS AND PRECAUTIONS**

#### 54 **5.1 Effects on Driving**

55 HORIZANT may cause significant driving impairment [*see Clinical Studies (14.3)*]. The  
56 duration of driving impairment after starting therapy with HORIZANT is unknown. Patients  
57 taking HORIZANT should not drive until they have gained sufficient experience to assess  
58 whether HORIZANT impairs their ability to drive. However, prescribers and patients should be  
59 aware that patients’ ability to assess their own driving competence, as well as their ability to  
60 assess the degree of somnolence caused by HORIZANT, can be imperfect. Whether the  
61 impairment is related to somnolence [*see Warnings and Precautions (5.2)*] or other effects of  
62 HORIZANT is unknown.

#### 63 **5.2 Somnolence/Sedation and Dizziness**

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

68 During the controlled trials in patients with RLS, somnolence/sedation was reported in  
69 20% of patients treated with 600 mg of HORIZANT per day compared with 6% of patients  
70 receiving placebo. In those patients treated with HORIZANT who reported somnolence, the  
71 somnolence persisted during treatment in about 30%. In the remaining patients, symptoms  
72 resolved within 3 to 4 weeks. Dizziness was reported in 13% of patients receiving 600 mg of  
73 HORIZANT per day compared with 4% of patients receiving placebo. In those patients treated  
74 with HORIZANT who reported dizziness, symptoms persisted during treatment in about 20%.  
75 Somnolence/sedation led to withdrawal in 2% of patients receiving 600 mg of HORIZANT per  
76 day. Dizziness led to withdrawal in 1% of patients receiving 600 mg of HORIZANT per day.  
77 The incidence of these adverse reactions was greater in the patients receiving 1,200 mg per day.

78 During the 12-week, controlled study in patients with PHN, somnolence was reported in  
79 10% of patients treated with 1,200 mg of HORIZANT per day compared with 8% of patients  
80 receiving placebo. Fatigue/asthenia was reported in 6% of patients treated with 1,200 mg of  
81 HORIZANT per day compared with 1% of patients receiving placebo. In those patients treated  
82 with 1,200 mg of HORIZANT per day who reported somnolence (10%), the somnolence  
83 persisted during treatment in about 27%. In the remaining patients, symptoms resolved within 4

84 to 5 weeks. Dizziness was reported in 17% of patients receiving 1,200 mg of HORIZANT per  
85 day compared with 15% of patients receiving placebo. In those patients treated with 1,200 mg of  
86 HORIZANT per day who reported dizziness, symptoms persisted during treatment in about 6%.  
87 Somnolence led to withdrawal in <1% of patients receiving 1,200 mg of HORIZANT per day  
88 compared with 2% of patients receiving placebo. Dizziness led to withdrawal in 2% of patients  
89 receiving 1,200 mg of HORIZANT per day compared with 3% of patients receiving placebo.

### 90 **5.3 Lack of Interchangeability With Gabapentin**

91 HORIZANT is not interchangeable with other gabapentin products because of differing  
92 pharmacokinetic profiles. The same dose of HORIZANT results in different plasma  
93 concentrations of gabapentin relative to other gabapentin products. [*See Clinical Pharmacology*  
94 (*12.3*).]

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

### 97 **5.4 Suicidal Behavior and Ideation**

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

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

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

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

123

124 **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

125  
126 The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy  
127 than in clinical trials for psychiatric or other conditions, but the absolute risk differences were  
128 similar for the epilepsy and psychiatric indications.

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

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

#### 140 **5.5 Drug Reaction With Eosinophilia and Systemic Symptoms** 141 **(DRESS)/Multiorgan Hypersensitivity**

142 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as  
143 multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including  
144 gabapentin. HORIZANT is a prodrug of gabapentin. Some of these events have been fatal or  
145 life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or  
146 lymphadenopathy, in association with other organ system involvement, such as hepatitis,  
147 nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute  
148 viral infection. Eosinophilia is often present. Because this disorder is variable in its expression,  
149 other organ systems not noted here may be involved.

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

## 154 **5.6 Discontinuation of HORIZANT**

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

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

## 162 **5.7 Tumorigenic Potential**

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

166 In clinical studies of gabapentin as adjunctive therapy in epilepsy comprising 2,085  
167 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients  
168 (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in*  
169 *situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up  
170 to 2 years following discontinuation of gabapentin. Without knowledge of the background  
171 incidence and recurrence in a similar population not treated with gabapentin, it is impossible to  
172 know whether the incidence reported in this cohort is or is not affected by treatment.

## 173 **6 ADVERSE REACTIONS**

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

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

### 177 **6.1 Clinical Trials Experience**

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

181 In all controlled and uncontrolled trials across various patient populations, more than  
182 2,300 patients have received HORIZANT orally in daily doses ranging from 600 to 3,600 mg.

183 **Restless Legs Syndrome:** The exposure to HORIZANT in 1,201 patients with RLS  
184 included 613 exposed for at least 6 months and 371 exposed for at least 1 year. HORIZANT in  
185 the treatment of RLS was studied primarily in placebo-controlled trials (n = 642), and in long-  
186 term follow-up studies. The population with RLS ranged from 18 to 82 years of age, with 60%  
187 being female and 95% being Caucasian.

188 The safety of HORIZANT in doses ranging from 600 to 2,400 mg has been evaluated in  
189 515 patients with RLS in 3 double-blind, placebo-controlled, 12-week clinical trials. The 600-mg  
190 dose was studied in 2 of the 3 studies. Eleven out of 163 (7%) patients treated with 600 mg of  
191 HORIZANT discontinued treatment due to adverse reactions compared with 10 of the 245 (4%)  
192 patients who received placebo.

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

197

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

Body System/Adverse Reaction	Placebo <sup>a</sup> (N = 245) %	HORIZANT 600 mg/day <sup>b</sup> (N = 163) %	HORIZANT 1,200 mg/day <sup>c</sup> (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

201 <sup>a</sup> Placebo was a treatment arm in each of the 3 double-blind, placebo-controlled, 12-week  
 202 clinical trials.

203 <sup>b</sup> The 600-mg dose of HORIZANT was a treatment arm in 2 of the 3 double-blind, placebo-  
 204 controlled, 12-week clinical trials.

205 <sup>c</sup> The 1,200-mg dose of HORIZANT was a treatment arm in each of the 3 double-blind,  
 206 placebo-controlled, 12-week clinical trials.

207

208 Adverse reactions reported in these three 12-week studies in <2% of patients treated with  
209 600 mg of HORIZANT and numerically greater than placebo were balance disorder, blurred  
210 vision, disorientation, feeling drunk, lethargy, and vertigo.

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

213 Postherpetic Neuralgia: The exposure to HORIZANT in 417 patients with PHN  
214 included 207 patients exposed for at least 3 months. Overall, the mean age of patients in the PHN  
215 studies ranged from 61 to 64 years of age across dose groups; the majority of patients were male  
216 (45% to 61%) and Caucasian (80% to 98%).

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

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

227

228 **Table 5. Incidence of Adverse Reactions (in At Least 2% of Patients Treated With**  
 229 **1,200 mg/day of HORIZANT and Numerically Greater Than the Placebo Rate)**  
 230 **Reported in All Patients in the 12-Week PHN Study**

Body System/Adverse Reaction	Placebo	HORIZANT	HORIZANT	HORIZANT
	(N = 95) %	1,200 mg/day (N = 107) %	2,400 mg/day (N = 82) %	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

231  
 232 The following adverse reactions were also reported as  $\geq 2\%$  at 2,400 mg/day and/or  
 233 3,600 mg/day and appeared to be dose-related but were  $< 2\%$  at 1,200 mg/day: balance disorder,  
 234 confusional state, depression, dry mouth, flatulence, increased appetite, irritability, and vertigo.  
 235 Dizziness, somnolence, fatigue, and insomnia appeared to show a dose relationship.

## 236 6.2 Adverse Events Associated With Gabapentin

237 The following adverse events have been reported in patients receiving gabapentin, either  
 238 in clinical trials or postmarketing: breast enlargement, gynecomastia, and elevated creatine  
 239 kinase.

## 240 7 DRUG INTERACTIONS

241 Gabapentin enacarbil is released faster from HORIZANT Extended-Release tablets in the  
 242 presence of alcohol. Consumption of alcohol is not recommended when taking HORIZANT [*see*  
 243 *Clinical Pharmacology (12.3)*].

244 Morphine: HORIZANT taken in conjunction with morphine causes increased  
 245 somnolence/sedation, dizziness, and nausea when compared with either drug alone [*see Clinical*  
 246 *Pharmacology (12.3)*].

247

**248 8 USE IN SPECIFIC POPULATIONS****249 8.1 Pregnancy**

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

255 When pregnant rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or  
256 5,000 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was increased  
257 at the 2 highest doses and fetal body weights were decreased at the high dose. The no-effect dose  
258 for embryo-fetal developmental toxicity in rats (200 mg/kg/day) represents approximately  
259 2 times the gabapentin exposure associated with the maximum recommended human dose  
260 (MRHD) of 1,200 mg/day gabapentin enacarbil on an area under the curve (AUC) basis.

261 When pregnant rabbits were administered gabapentin enacarbil (oral doses of 200, 500,  
262 or 2,500 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was  
263 increased and fetal body weights were decreased at the high dose. The no-effect dose for  
264 embryo-fetal developmental toxicity in rabbits (500 mg/kg/day) represents approximately  
265 9 times the gabapentin exposure associated with the MRHD of 1,200 mg/day gabapentin  
266 enacarbil on an AUC basis.

267 When female rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or  
268 5,000 mg/kg/day) throughout the pregnancy and lactation periods, offspring growth and survival  
269 were decreased at the two highest doses. The no-effect dose for pre- and post-natal  
270 developmental toxicity in rats is approximately 2 times the MRHD on an AUC basis.

271 In reproductive and developmental studies of gabapentin, developmental toxicity was  
272 observed at all doses tested. Increased incidences of hydroureter and/or hydronephrosis were  
273 observed in rat offspring following treatment of pregnant animals in studies of fertility and  
274 general reproductive performance, embryo-fetal development, and peri- and post-natal  
275 development. Overall, a no-effect dose was not established. In mice, treatment of pregnant  
276 animals with gabapentin during the period of organogenesis resulted in delayed fetal skeletal  
277 ossification at all but the lowest dose tested. When pregnant rabbits were treated with gabapentin  
278 during the period of organogenesis, an increase in embryo-fetal mortality was observed at all  
279 doses of gabapentin tested.

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

287 **8.2 Labor and Delivery**

288 The effect of HORIZANT on labor and delivery is unknown.

289 **8.3 Nursing Mothers**

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

295 **8.4 Pediatric Use**

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

297 **8.5 Geriatric Use**

298 Of the 515 patients treated with HORIZANT in the 3 double-blind, placebo-controlled,  
 299 12-week clinical trials for RLS, 11% were 65 to 74 years of age and 1% were 75 years of age  
 300 and older. Clinical trials of HORIZANT for the treatment of RLS did not include a sufficient  
 301 number of patients 65 years and older to determine whether they respond differently from  
 302 younger individuals.

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

311 Gabapentin is known to be almost exclusively excreted by the kidney, and the risk of  
 312 adverse reactions to this drug may be greater in patients with impaired renal function. Because  
 313 elderly patients are more likely to have decreased renal function, the frequency of dosing may  
 314 need to be adjusted based on calculated creatinine clearance in these patients [*see Dosage and*  
 315 *Administration (2.3)*].

316 **8.6 Renal Impairment**

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

319 **9 DRUG ABUSE AND DEPENDENCE**

320 **9.1 Controlled Substance**

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

322 **9.2 Abuse**

323 Gabapentin does not exhibit affinity for benzodiazepine, opiate ( $\mu$ ,  $\delta$ , or  $\kappa$ ), or  
 324 cannabinoid 1 receptor sites. A small number of postmarketing cases report gabapentin misuse  
 325 and abuse. These individuals were taking higher than recommended doses of gabapentin for

326 unapproved uses. Most of the individuals described in these reports had a history of poly-  
327 substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances.

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

### 331 **9.3 Dependence**

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

## 339 **10 OVERDOSAGE**

### 340 **10.1 Human Overdose Experience**

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

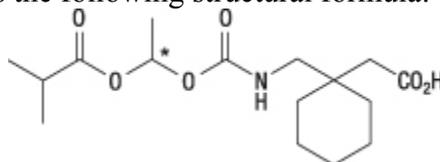
### 346 **10.2 Overdosage Management**

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

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

## 354 **11 DESCRIPTION**

355 HORIZANT (gabapentin enacarbil) is a prodrug of gabapentin. Gabapentin enacarbil is  
356 described as (1-{{((1*RS*)-1-[(2-Methylpropanoyl)oxy]ethoxy}carbonyl)amino]methyl}  
357 cyclohexyl) acetic acid. It has a molecular formula of C<sub>16</sub>H<sub>27</sub>NO<sub>6</sub> and a molecular weight of  
358 329.39. It is a racemate and has the following structural formula:



359

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

363 HORIZANT is administered orally. Each HORIZANT Extended-Release Tablet contains  
364 300 mg or 600 mg of gabapentin enacarbil and the following inactive ingredients: colloidal  
365 silicon dioxide, dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium stearate,  
366 sodium lauryl sulfate, and talc. The 300 mg tablets also contain red ferric oxide.

## 367 **12 CLINICAL PHARMACOLOGY**

### 368 **12.1 Mechanism of Action**

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

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

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

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

385 *In vitro* studies have shown that gabapentin binds with high affinity to the  $\alpha 2\delta$  subunit of  
386 voltage-activated calcium channels; however, the relationship of this binding to the therapeutic  
387 effects of gabapentin enacarbil in RLS and PHN is unknown.

### 388 **12.3 Pharmacokinetics**

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

393 For subjects with PHN taking HORIZANT 600 mg twice daily, the estimated steady state  
394 mean  $C_{\max}$  was 5.35  $\mu\text{g/mL}$ , mean  $\text{AUC}_{24}$  was approximately 109  $\mu\text{g}\cdot\text{hr/mL}$ , mean  $C_{\min}$  was  
395 3.63  $\mu\text{g/mL}$ , and mean peak trough ratio was 1.5.

396 **Absorption:** The pathway for absorption of gabapentin enacarbil is believed to include  
397 active transport via a proton-linked monocarboxylate transporter, MCT-1. This transporter is  
398 expressed at high levels in the intestinal tract and is not saturated by administration of high doses

399 of HORIZANT. Mean bioavailability of gabapentin (based on urinary recovery of gabapentin)  
400 for HORIZANT in the fed state is about 75%. Bioavailability under fasting conditions has been  
401 estimated by gabapentin urinary recovery to be 42% to 65%. In a food effect study, the exposure  
402 of gabapentin increased by 24%, 34%, and 44% with low, moderate, and high fat meals,  
403 respectively. The  $T_{max}$  of gabapentin after administration of 600 mg of HORIZANT was  
404 5.0 hours in fasted subjects and 7.3 hours in fed subjects. Steady state is reached in 2 days with  
405 daily administration.

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

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

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

422 Apparent oral clearance (CL/F) of gabapentin from plasma after dosing of HORIZANT  
423 with food ranged from 6.0 to 9.3 L/hr. Following oral dosing of HORIZANT, plasma clearance  
424 of gabapentin is approximately proportional to creatinine clearance. Renal clearance (CL<sub>r</sub>) of  
425 gabapentin ranged from 5 to 7 L/hr, regardless of food intake or food type. The elimination  
426 half-life ( $t_{1/2}$ ) of gabapentin ranges from 5.1 to 6.0 hours and is unaltered by dose or following  
427 multiple doses of HORIZANT.

428 **Special Populations:** **Race:** In the population pharmacokinetic study, the majority  
429 (94%) of subjects in the clinical studies was Caucasian, and no single other race was greater than  
430 4%; therefore, the effect of race could not be studied.

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

433 **Geriatric Patients:** There are no clinically significant differences in pharmacokinetics  
434 of HORIZANT between geriatric patients ( $\geq 65$  years of age) and younger patients (18 to  
435 <65 years of age). However, the pharmacokinetics in geriatric patients may be affected by an  
436 age-related decline in renal function [*see Use in Specific Populations (8.5)*].

437 **Renal Impairment:** Gabapentin clearance after dosing with HORIZANT is  
438 approximately proportional to CrCl. Apparent oral clearance (CL/F) decreased in moderate

439 (4.2 L/hr) and severe renal impairment patients (1.7 L/hr) compared with 6.0 to 9.3 L/hr in  
440 patients without renal impairment. Similarly, CL<sub>r</sub> was decreased to 3 and 1 L/hr in moderate and  
441 severe renal impairment patients, respectively, compared with 5 to 7 L/hr in non-renal  
442 impairment patients. Dosage reduction in patients with renal dysfunction not on dialysis is  
443 necessary.

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

450 **Drug Interactions:** Neither gabapentin enacarbil nor gabapentin are substrates,  
451 inhibitors, or inducers of the major cytochrome P450 enzymes. Gabapentin enacarbil is neither a  
452 substrate or an inhibitor of P-glycoprotein *in vitro*.

453 Pharmacokinetic drug-drug interaction studies were conducted to examine the potential  
454 for an interaction of gabapentin enacarbil with cimetidine and naproxen. No significant  
455 pharmacokinetic interactions were observed. No clinically relevant pharmacokinetic interactions  
456 are expected between HORIZANT and other substrates of organic cation transporter type 2  
457 (OCT2) and monocarboxylate transporter type 1 (MCT-1).

458 ***Ethanol:*** An *in vitro* dissolution study was conducted to evaluate the impact of ethanol  
459 (5, 10, 20, and 40%), on the extended-release characteristics of HORIZANT. The *in vitro* study  
460 showed that about 63% of the total gabapentin enacarbil dose was released at 1 hour at the  
461 highest alcohol level (40%), and about 43% of total drug was released at 1 hour with 5% alcohol.  
462 Ethanol causes a more rapid release of gabapentin enacarbil from the extended-release tablets  
463 that may increase the risk for adverse events associated with HORIZANT. Consumption of  
464 alcohol is not recommended when taking HORIZANT.

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

472 ***Naproxen:*** The pathway for absorption of gabapentin enacarbil includes active  
473 transport via a proton-linked MCT-1. Coadministration of 1,200 mg of HORIZANT once daily  
474 with naproxen 500 mg twice daily, a known substrate of MCT-1, showed no effect on naproxen  
475 exposure or steady-state gabapentin C<sub>max</sub> and AUC. No clinically relevant pharmacokinetic  
476 interactions are expected between HORIZANT and other substrates of MCT-1.

477 ***Morphine:*** Administration of a single 600-mg dose of HORIZANT 2 hours after a  
478 single 60-mg dose of extended-release morphine sulfate in 18 subjects was associated with

479 increased somnolence/sedation, dizziness, and nausea for the combination compared to Horizant  
480 or morphine alone as measured by the visual analog scale. No changes in  $C_{max}$  and AUC of  
481 gabapentin, morphine or its active metabolite morphine-6-glucuronide were observed.

## 482 **13 NONCLINICAL TOXICOLOGY**

### 483 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

484 Carcinogenesis: Oral (gavage) carcinogenicity studies were conducted in mice and rats.  
485 In mice, gabapentin enacarbil was tested at doses of 500, 2,000, or 5,000 mg/kg/day for up to  
486 104 weeks. There was no evidence of drug-related carcinogenicity. The highest dose tested is  
487 16 times the MRHD of 1,200 mg/day, on a plasma AUC basis.

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

493 In 2-year dietary carcinogenicity studies of gabapentin, no evidence of drug-related  
494 carcinogenicity was observed in mice treated at doses up to 2,000 mg/kg/day. In rats, increases in  
495 the incidence of pancreatic acinar cell adenoma and carcinoma were found in male rats receiving  
496 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,  
497 the plasma AUC for gabapentin is estimated to be approximately 13 times that in humans at the  
498 MRHD.

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

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

511 Impairment of Fertility: Oral administration of gabapentin enacarbil (doses of 0, 200,  
512 1,000, or 5,000 mg/kg/day) to male and female rats prior to and throughout mating and  
513 continuing in females up to day 7 of gestation resulted in no adverse effects on fertility. The  
514 highest dose tested is approximately 39 times the MRHD on an AUC basis.

**515 14 CLINICAL STUDIES****516 14.1 Restless Legs Syndrome (RLS) 12-Week Pivotal Studies**

517 The effectiveness of HORIZANT in the treatment of moderate-to-severe primary RLS  
518 was demonstrated in two 12-week clinical studies in adults diagnosed with RLS using the  
519 International Restless Legs Syndrome Study Group diagnostic criteria. Key diagnostic criteria  
520 for RLS are: an urge to move the legs usually accompanied or caused by uncomfortable and  
521 unpleasant leg sensations, symptoms begin or worsen during periods of rest or inactivity such as  
522 lying or sitting, symptoms are partially or totally relieved by movement such as walking or  
523 stretching at least as long as the activity continues, and symptoms are worse or occur only in the  
524 evening or night. Patients were required to have a total score of  $\geq 15$  on the International Restless  
525 Legs Syndrome (IRLS) Rating Scale at baseline. Patients with RLS secondary to other  
526 conditions (e.g., pregnancy, renal failure, iron deficiency anemia) were excluded. In study 1,  
527 patients were randomized to receive 1,200 mg of HORIZANT (N = 112) or placebo (N = 108)  
528 taken once daily at about 5 PM with food. In study 2, patients were randomized to receive  
529 600 mg of HORIZANT (N = 114), 1,200 mg of HORIZANT (N = 111), or placebo (N = 96)  
530 taken once daily at about 5 PM with food.

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

541 In these 2 studies, the mean age of patients studied was 50 years (range: 18 to 81 years);  
542 59% of the patients were female. The racial distribution for these studies was as follows:  
543 Caucasian, 95%; black, 2%; and other, 3%.

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

549

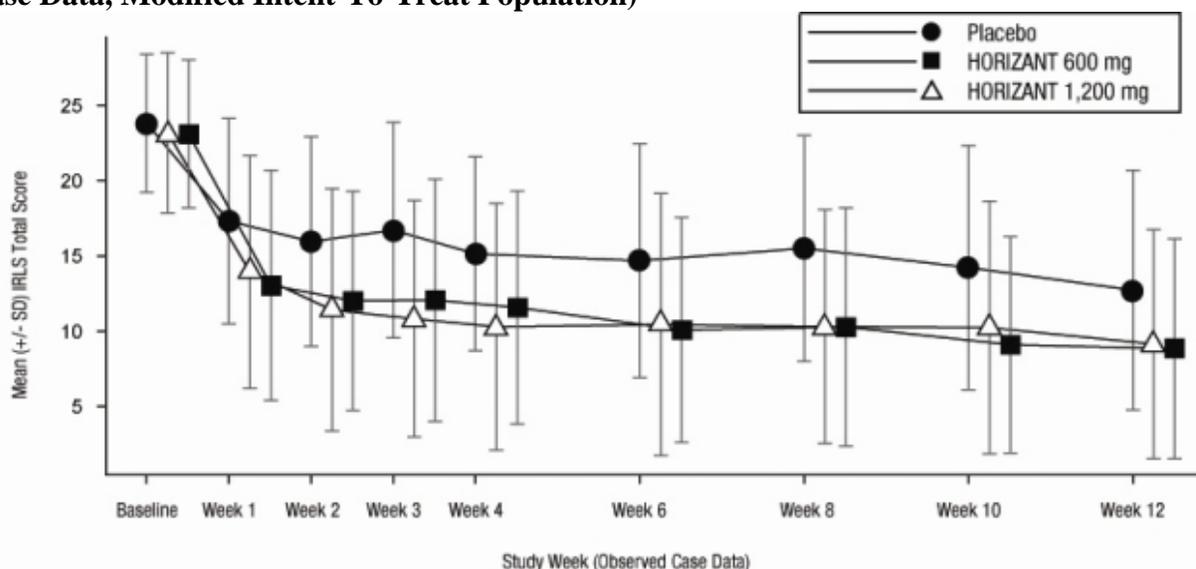
550 **Table 6. Mean Change in IRLS Scale Total Score and Proportion of Responders on CGI-I**  
 551 **Scale at Week 12**

Week 12	Study 1		Study 2		
	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 <sup>a</sup> on CGI-I	76%	39%	73%	77%	45%

552 <sup>a</sup> CGI-I Responders = “much improved” and “very much improved.”

553  
 554 Figure 1 presents the improvement in mean IRLS Rating Scale total score in patients  
 555 treated with placebo or 600 or 1,200 mg of HORIZANT over the 12 weeks of treatment in  
 556 study 2.

557  
 558 **Figure 1. Study 2, Mean (±SD) IRLS Rating Scale Total Score Over 12 Weeks (Observed**  
 559 **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

560  
 561  
 562 **14.2 Postherpetic Neuralgia (PHN) 12-Week Study**

563 The efficacy of HORIZANT for the management of postherpetic neuralgia was  
 564 established in a multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-  
 565 week study evaluating the efficacy, safety, and dose response of 3 maintenance doses of  
 566 HORIZANT (1,200, 2,400, and 3,600 mg/day, with 107, 82, and 87 patients in each dosing  
 567 group, respectively). Patients greater than 18 years of age with a documented medical diagnosis

568 of PHN of at least three months duration were enrolled. To ensure that patients had significant  
 569 pain, randomized patients were required to have a minimum baseline 24-hour average Pain  
 570 Intensity Numerical Rating Scale (PI-NRS) intensity score of at least 4.0 on the 11-point  
 571 numerical PI-NRS, ranging from 0 (“no pain”) to 10 (“pain as bad as you can imagine”).

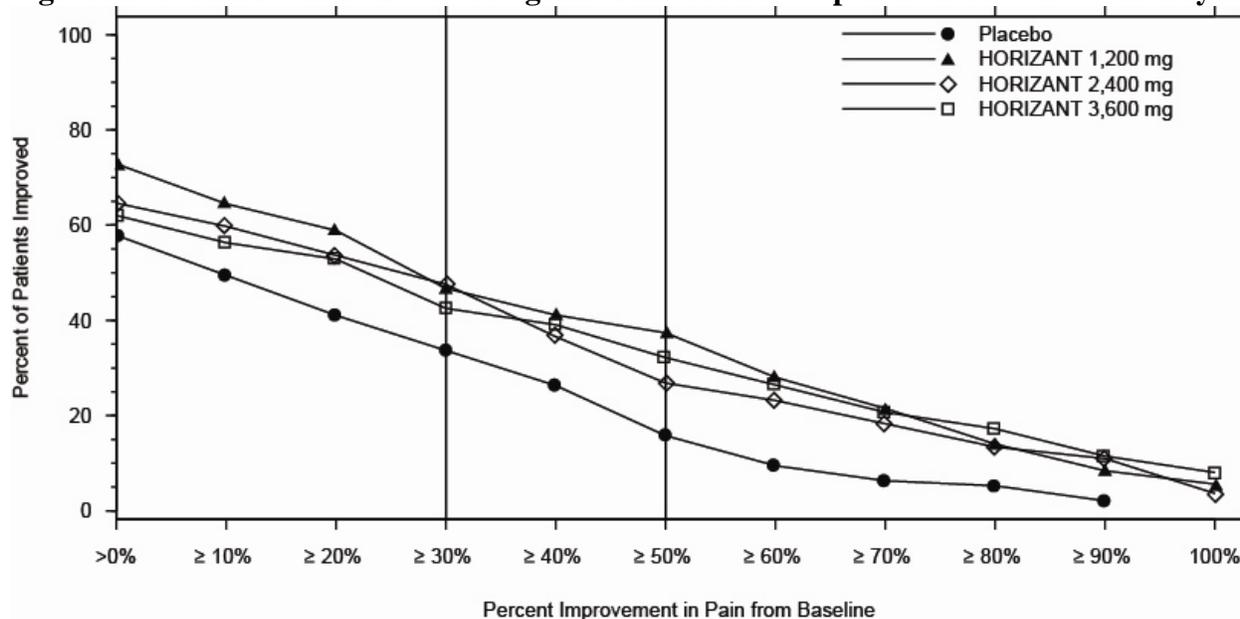
572 In this study, a total of 276 patients received HORIZANT while 95 patients received  
 573 placebo. Following a 1-week baseline period during which patients were screened for eligibility,  
 574 patients began a 1-week up-titration period followed by a 12-week maintenance treatment  
 575 period,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

576 Treatment with HORIZANT statistically significantly improved the mean pain score and  
 577 increased the proportion of patients with at least a 50% reduction in pain score from baseline at  
 578 all doses tested. A benefit over placebo was observed for all 3 doses of HORIZANT as early as  
 579 Week 1 and maintained to the end of treatment. Additional benefit of using doses of greater than  
 580 1,200 mg a day was not demonstrated.

581 For various degrees of improvement in pain from baseline to end of maintenance  
 582 treatment, Figure 2 shows the fraction of patients achieving that degree of improvement. The  
 583 figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also  
 584 included at every level of improvement below 50%. Patients who did not complete the study  
 585 were assigned 0% improvement.

586  
 587

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



588  
 589

**14.3 Effects on Driving**

591 Driving performance was assessed in a three way crossover study in healthy volunteers  
 592 (mean age 36 years). Subjects were dosed at approximately 5 pm with HORIZANT 600 mg (for  
 593 five days), diphenhydramine 50 mg (1 dose), and placebo (for five days). After the last dose,

594 driving was evaluated on a computer-based simulation for 1 hour in the evening approximately 2  
 595 to 4 hours after dosing (7 to 9 pm), in the morning after dosing (7 to 9 am), and at midday the  
 596 day after dosing (11 am to 1pm). The primary endpoint of the study was lane position variability.  
 597 There was no difference in change from baseline in lane position variability for HORIZANT  
 598 compared to placebo at any of the simulated driving timepoints. Secondary measures included  
 599 speed variability and the occurrence of simulated crashes. Subjects in this study experienced  
 600 simulated crashes as described in Table 7. At the times that simulated crashes occurred, there  
 601 was an increase in average speed variability in the HORIZANT and diphenhydramine treated  
 602 groups that was most notable in patients who experienced simulated crashes, but no increases in  
 603 lane position variability. Later time points post-dosing or the effects of driving after more than  
 604 five days of dosing with HORIZANT were not evaluated.

605

606 **Table 7. Simulated Crashes at Evaluated Timepoints (Secondary Measure)**

<b>Simulated Driving Timepoint and Hours Post Dose</b>	<b>Baseline N = 36 n (%)</b>	<b>Placebo N = 36 n (%)</b>	<b>HORIZANT 600 mg N = 35 n (%)</b>	<b>Diphenhydramine 50 mg N = 36 n (%)</b>
<b>Day 5</b> Evening (7 to 9pm) 2 to 4 hours post dose	0 (0)	0 (0)	0 (0)	3 (9)
<b>Day 6</b> Morning (7 to 9am) 14 to 16 hours post dose	2 (6)	1 (3)	1 (3)	0 (0)
<b>Day 6</b> Midday (11am to 1pm) 18 to 20 hours post dose	1 (3)	0 (0)	3 (9)	3 (8)

607

608 The results of a separate 2-week driving simulation study in patients (mean age 47 years)  
 609 with moderate-to-severe primary RLS showed that once daily doses of 1,200 mg and 1,800 mg  
 610 of HORIZANT significantly impaired simulated driving performance based on lane position  
 611 variability. An increased number of simulated crashes were reported in patients tested near  $T_{max}$   
 612 after receiving 1,200 mg or 1,800 mg of HORIZANT compared to patients treated with  
 613 diphenhydramine 50 mg. In addition patients receiving 1,200 mg of HORIZANT experienced an  
 614 increased number of simulated crashes at 14 to 16 hours after dosing compared with placebo,  
 615 diphenhydramine, and 1,800 mg of HORIZANT.

616 The design limitations of these two studies do not permit inference regarding dose  
 617 response relationship or the duration of the effect HORIZANT has on driving in patients with  
 618 RLS.

619 The results of a separate driving simulation study comparing untreated RLS patients and  
 620 healthy subjects showed no difference in lane position variability but an increase in speed

621 variability associated with a greater number of simulated crashes in RLS patients relative to  
622 healthy subjects, which may indicate impaired driving in RLS patients in the absence of  
623 medication.

## 624 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

630 300 mg: NDC 0173-0832-13: Bottles of 30

631 600 mg: NDC 0173-0806-01: Bottles of 30

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

## 634 **17 PATIENT COUNSELING INFORMATION**

635 *See FDA-approved patient labeling (Medication Guide).*

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

### 639 **17.1 Effects on Driving**

640 Patients should be told that HORIZANT may cause a significant driving impairment.  
641 Accordingly, they should be advised not to drive a car until they have gained sufficient  
642 experience on HORIZANT to assess whether HORIZANT impairs their ability to drive, although  
643 patients’ ability to determine their level of impairment can be unreliable. Patients should be told  
644 that it is not known how long this effect lasts.

### 645 **17.2 Somnolence/Sedation and Dizziness**

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

### 651 **17.3 Suicidal Behavior and Ideation**

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

657 **17.4 Drug Reaction With Eosinophilia and Systemic Symptoms**  
658 **(DRESS)/Multiorgan Hypersensitivity**

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

662 **17.5 Lack of Interchangeability With Gabapentin**

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

665 **17.6 Dosing Instructions**

- 666 • Instruct patients to take HORIZANT only as prescribed.  
667 • Instruct patients to swallow tablets whole and do not cut, crush, or chew tablets.  
668 • Instruct patients to take HORIZANT with food.  
669 • For Restless Legs Syndrome, 600 mg HORIZANT should be taken once daily at about 5 PM.  
670 If the dose is not taken at the recommended time, the patient should take the next dose at  
671 about 5 PM the following day.  
672 • For Postherpetic Neuralgia, the starting dose is 600 mg HORIZANT in the morning for  
673 3 days. Starting on day 4, 600 mg HORIZANT should be taken twice daily. If the dose is not  
674 taken at the recommended time, the next dose should be taken at the time of next scheduled  
675 dose.  
676 • Instruct patients about how to discontinue HORIZANT.

677 **17.7 Alcohol**

- 678 • Advise patients to avoid alcohol when taking HORIZANT [see *Drug Interactions (7)*;  
679 *Clinical Pharmacology (12.3)*].  
680

681 HORIZANT is a registered trademark of GlaxoSmithKline.

682  
683 Manufactured by:

684 Patheon Inc.

685 Research Triangle Park, NC 27709

686

for:



GlaxoSmithKline  
Research Triangle Park, NC 27709

Licensed from:



XenoPort, Inc.  
Santa Clara, CA 95051

687

688 ©2013, GlaxoSmithKline. All rights reserved.

689

690 HZT:XPI

691 **PHARMACIST—DETACH HERE AND GIVE TO PATIENT**

692

-----

693 **MEDICATION GUIDE**  
694 **HORIZANT®** (*ho-ri' zant*)  
695 **(gabapentin enacarbil)**  
696 **Extended-Release Tablets**

697

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

701

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

703 **HORIZANT can cause serious side effects:**

704 **1. Do not drive after taking your dose of HORIZANT until you know how**  
705 **HORIZANT affects you, including the morning after you take your dose.**

706 **Do not** operate heavy machinery or do other dangerous activities until you  
707 know how HORIZANT affects you. HORIZANT can cause sleepiness, dizziness,  
708 slow thinking, and can affect your coordination. Ask your healthcare provider  
709 when it would be okay to do these activities.

710 **2. HORIZANT may cause suicidal thoughts or actions in a very small**  
711 **number of people, about 1 in 500.**

712 **Call a healthcare provider right away if you have any of these**  
713 **symptoms, especially if they are new, worse, or worry you:**

- 714 • thoughts about suicide or dying
- 715 • attempt to commit suicide
- 716 • new or worse depression
- 717 • new or worse anxiety
- 718 • feeling agitated
- 719 • new or worse restlessness
- 720 • panic attacks
- 721 • new or worse trouble sleeping (insomnia)
- 722 • new or worse irritability
- 723 • acting aggressive, being angry, or violent
- 724 • acting on dangerous impulses
- 725 • an extreme increase in activity and talking (mania)
- 726 • other unusual changes in behavior or mood

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

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

733 **Do not stop HORIZANT without first talking to a healthcare provider.**

734 Suicidal thoughts or actions can be caused by things other than medicines. If  
735 you have suicidal thoughts or actions, your healthcare provider may check for  
736 other causes.

737 **3. HORIZANT may cause a serious or life-threatening allergic reaction** that  
738 may affect your skin or other parts of your body such as your liver or blood  
739 cells. You may or may not have rash with these types of reactions. Call a  
740 healthcare provider right away if you have any of the following symptoms:

- 741 • skin rash  
742 • hives  
743 • fever  
744 • swollen glands that do not go away  
745 • swelling of your lips or tongue  
746 • yellowing of your skin or eyes  
747 • unusual bruising or bleeding  
748 • severe fatigue or weakness  
749 • unexpected, severe muscle pain  
750 • frequent infections

751  
752 These symptoms may be the first signs of a serious reaction. A healthcare provider  
753 should examine you to decide if you should continue taking HORIZANT.

754  
755 **What is HORIZANT?**

756 HORIZANT is a prescription medicine used to treat adults with:

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

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

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

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

765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803

**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.
- 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.
- drink alcohol.

**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.

804 **What should I avoid while taking HORIZANT?**

- 805 • Do not take other medicines that make you sleepy or dizzy while taking  
806 HORIZANT without first talking with your healthcare provider. Taking HORIZANT  
807 with medicines that cause sleepiness or dizziness may make your sleepiness or  
808 dizziness worse.
- 809 • Do not take other gabapentin drugs (for example, NEURONTIN or GRALISE)  
810 while you take HORIZANT.
- 811 • Do not consume alcohol when taking HORIZANT.

812

813 **What are the possible side effects of HORIZANT?**

- 814 • See **“What is the most important information I should know about**  
815 **HORIZANT?”**

816 The most common side effects of HORIZANT include:

- 817 • sleepiness  
818 • dizziness  
819 • headache

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

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

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

826

827 **How should I store HORIZANT?**

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

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

833

834 **General Information about the safe and effective use of HORIZANT**

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

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

841 You can ask your healthcare provider or pharmacist for information about  
842 HORIZANT that was written for healthcare professionals.  
843 For more information about HORIZANT, go to [www.gsk.com](http://www.gsk.com) or call 1-888-825-  
844 5249.

845  
846 **What are the ingredients in HORIZANT?**

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

852  
853 **This Medication Guide has been approved by the U.S. Food and Drug**  
854 **Administration.**

855  
856 Manufactured by:  
857 Patheon Inc.  
858 Research Triangle Park, NC 27709  
859

for:



GlaxoSmithKline  
Research Triangle Park, NC 27709

Licensed from:



XenoPort, Inc.  
Santa Clara, CA 95051

860  
861 Revised: 03/2013  
862

863 HORIZANT is a registered trademark of GlaxoSmithKline. The other brands listed  
864 are trademarks of their respective owners and are not trademarks of  
865 GlaxoSmithKline. The makers of these brands are not affiliated with and do not  
866 endorse GlaxoSmithKline or its products.

867  
868 ©2013, GlaxoSmithKline. All rights reserved.

869  
870 HZT: XMG

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022399Orig1s005**

**SUMMARY REVIEW**

## MEMORANDUM

DATE: March 26, 2013

FROM: Director  
Division of Neurology Products/HFD-120

TO: File, NDA 022399/S-005

SUBJECT: Action Memo for NDA 022399/S-005, a Labeling Supplement for Horizant (gabapentin enacarbil) Extended-Release Tablets to include the results of a simulated driving study in product labeling

NDA 022399/S-005, a Labeling Supplement for Horizant (gabapentin enacarbil) Extended-Release Tablets to include the results of a simulated driving study in product labeling, was submitted by Glaxo Group Limited on 2/29/12. This supplement was submitted in fulfillment of a Post Marketing Requirement (PMR), issued in the 4/6/11 Approval letter for Horizant for the treatment of Restless Legs Syndrome (RLS). In the original application for Horizant for RLS, the sponsor had submitted the results of a simulated driving study comparing daily doses of Horizant of 1200 mg and 1800 mg and diphenhydramine. The results of that study demonstrated adverse effects of both doses of Horizant, though the 1200 mg dose was seen to be worse than the 1800 mg dose. The results of this study were described in product labeling, though the recommended daily dose was (is) 600 mg, a dose that was not included in the driving study.

Because of the results of that study, and because the 600 mg dose is known to cause sedation, the Approval letter contained a PMR for a simulated driving study evaluating the 600 mg dose. The sponsor has submitted the results of such a study. In addition, the sponsor has submitted the results of a study evaluating the pharmacokinetic/pharmacodynamic (PK/PD) interactions between Horizant and morphine. This latter study was also a PMR described in the 4/6/11 Approval letter.

This supplement has been reviewed by Dr. Susanne Goldstein, medical reviewer, Dr. Tristan Massie, statistician, Drs. Veneeta Tandon and Atul Bhattaram, Office of Clinical Pharmacology, and Dr. Dave Podskalny, neurology team leader and Cross-Discipline Team Leader (CDTL). The clinical review team recommends that the supplement be approved with the inclusion of language in labeling describing the results of the driving simulation study and the interaction study with morphine. The division and the sponsor have agreed to labeling changes.

I will very briefly describe the results of the two studies and offer the rationale for the division's action.

## Driving Study

Drs. Massie, Goldstein, and Podskalny have clearly described the design and results of the simulated driving study.

The study was a three-period cross-over study in which patients received a single dose of Horizant 600 mg, diphenhydramine 50 mg, or placebo, at 5PM for 5 days in each treatment period. Each treatment period was 6 days, separated by a 2 day washout. Simulated driving performance was assessed (on computer screen, not a self-contained simulator) in each period at Day -1 at 7-9 PM, Day 1 at 7-9 AM, Day 5 at 7-9 PM (evening), and Day 6 at 7-9 AM (morning) and 11 AM-1 PM (mid-day), for about one hour at each assessment. These times were chosen to assess driving performance at the times when patients would be most likely to drive (i.e., in the early evening after dosing, and the next morning and afternoon). The Tmax of gabapentin is about 7 hours, so the testing was not performed at Tmax, by design.

The primary outcome was Lane Position Variability (LPV), defined as the difference (in feet) between the center of the “vehicle” and the center line of a 26 foot wide roadway (a negative difference indicates that the “vehicle” has crossed the center line).

Other outcomes assessed included crashes (defined as a collision with an oncoming car or an event where the distance between the “vehicle” and the center line was greater than 18 feet [on either side of the road]), and speed variability.

## Results

A total of 36 healthy volunteers were enrolled, and 35 completed.

### LPV

On mean change from baseline on LPV, at the Day 5 evening assessment, there were no differences between the Horizant and placebo groups, but there was numerical worsening between diphenhydramine and both the placebo and Horizant groups.

At the Day 6 morning assessment, there were no meaningful differences between any of the treatment groups.

At the Day 6 mid-day assessment, there were no meaningful differences among the three groups.

The sponsor also evaluated the incidence of “extreme” LPV values, defined as those that were in the top 5-15% and the top 5%. Only the diphenhydramine

group, at Day 5 at the evening assessment, had a clear increase compared to placebo in the percent of patients in the top 5%.

### Crashes

At Day 5, at the evening assessment, 3 subjects under diphenhydramine treatment had crashes (2 subjects had 1 crash each, one had 2 crashes). At Day 6, at the mid-day assessment, 3 subjects had crashes under Horizant treatment (2 subjects had one crash each, one subject had 2 crashes), and 3 subjects (one crash each) had crashes under diphenhydramine treatment.

### Speed Variability (SV)

Although there were differences between Horizant and placebo in mean change from baseline in SV on Day 5 and Day 6 at the mid-day assessments, these differences were small. There was a clear difference in mean change from baseline in SV between diphenhydramine and placebo (and Horizant) at the Day 5 evening assessment.

### Morphine Interaction Study

A three-period cross-over study in 18 healthy males compared the PK/PD of single doses of morphine 60 mg, Horizant 600 mg, and the combination (Horizant was administered 2 hours after morphine). There were no important PK interactions. However, Visual Analogue Scales (VAS) showed an increase in somnolence, dizziness, and nausea with the combination compared to the individual drugs.

### Comments

The sponsor has submitted a simulated driving study that showed no difference between Horizant 600 mg and placebo at any time point on the primary outcome of LPS. The study did show an effect of the positive control, diphenhydramine on LPS in the evening after dosing. Based largely on this result, the sponsor argues that the study documents a lack of effect of Horizant 600 mg on driving.

However, there was an increase in the number of subjects who experienced crashes in the Horizant 600 mg period compared to placebo (3 vs 0) at the mid-day assessment on Day 6. The number of subjects who crashed in this period was the same as the number of patients who crashed during diphenhydramine at the evening assessment on Day 5, (which, as noted, was also the time point at which these subjects had an increase in LPV) and at the mid-day assessment on Day 6.

The sponsor argues that it is impossible to interpret crashes in the context of no changes in the primary outcome of LPV, the number of events is small, subjects

had crashes at baseline (2 subjects had crashes at the Day 6 morning assessment and 1 had a crash at the Day 6 mid-day assessment), and that post-marketing data do not indicate that Horizant is associated with crashes.

There were no correlations between plasma levels of gabapentin and any driving measure.

Although I agree that the number of crashes is small, and that there a few crashes seen at baseline, it is difficult to dismiss the crashes seen at the Day 6 mid-day assessment in the Horizant treatment period. The number of crashes was the same (N=3) as that seen at several time points under diphenhydramine treatment, a known positive control that did show an effect at one time point on the primary outcome. Further, we are aware that 600 mg of Horizant is a sedating dose is some patients. Although it is not clear why an effect on driving should be seen at the Day 6 mid-day assessment for Horizant (the Tmax is about 7 hours), it should be remembered that the study was quite small, and, in any event, we do not have a good understanding of the time course of the pharmacodynamic responses to treatment. It should also be noted that, although there was a lack of correlation between gabapentin plasma levels and performance in this study, these studies are typically too small to show a clear correlation of plasma levels and performance. It is likely to be true that individual patients do have individual exposure-responses for adverse events.

For these reasons, we have concluded that the study (especially in conjunction with the previous driving study of Horizant 1200 and 1800 mgs) provides evidence that Horizant 600 mg, given at 5 PM, can increase the risk for impaired driving the next day.

(b) (4)

We have agreed with the sponsor to revise the already existing language in the Warnings and Precautions section of labeling, and to add extensive language in Section 14 that describes the results of the new driving study. Additional language has been added to the Information for Patients section of labeling. We have further agreed to add language in the Drug Interactions and Clinical Pharmacology sections of labeling describing the interaction with morphine.

For these reasons, I will issue the attached Approval letter for Supplement 5, with the appended agreed-upon product labeling.

Russell Katz, M.D.

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

/s/  
-----

RUSSELL G KATZ  
03/27/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022399Orig1s005**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	03/06/2013
<b>From</b>	Gerald D. Podskalny, DO, MS
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # Supplement#</b>	NDA 22399 Supp # 5, 6, 7
<b>Applicant</b>	GLAXO GROUP LTD
<b>Date of Submission</b>	02/29/2012
<b>PDUFA Goal Date</b>	12/29/2012
<b>Proprietary Name / Established (USAN) names</b>	Horizant/Gabapentin enacarbil
<b>Dosage forms / Strength</b>	Tablet/600 mg
<b>Proposed Indication(s)</b>	1. Moderate to severe primary Restless Legs Syndrome
<b>Recommended:</b>	<i>Approval</i>

This review was amended to remove the “Draft” watermark.

## 1. Introduction

The original NDA for Horizant [gabapentin enacarbil (GEN)] was approved on April 4, 2011, for the treatment of patients with moderate to severe Primary Restless Legs Syndrome (RLS). Studies XP-088 and XP-083 assessed the potential effect of GEN on driving and were included in the NDA submission. Results from these two studies assessed simulated driving performance. Study XP-088 compared simulated driving performance in patients with RLS to healthy subjects. The primary outcome was mean Lane Position Variability (LPV). In this study, patients with RLS had a greater number of crashes compared to healthy subjects. Study (XP083) was an active control, parallel groups study that compared simulated driving performance in patients with RLS who were treated with GEN 1200 mg and 1800 mg once daily for 2 weeks to a single dose of 50 mg diphenhydramine. The study demonstrated that patients with RLS treated with 1200 mg and 1800 mg of GEN had impaired simulated driving performance (crashes). The results indicated there was an increase in the number of crashes and mean LPV in patients treated with 1200 mg (less severe in patients receiving 1800 mg) compared to baseline for driving assessments performed near T<sub>max</sub> for GEN. The specific driving impairments observed in study XP083 included LPV and increased simulated crashes for the for patients treated with 1200 mg when they were dosed at 10 AM-1 PM and tested at 7 AM the next morning (Day 15). However, in the same study patients treated with 1800 mg of GEN had little signs of impaired driving. The Agency approved the 600 mg dose of GEN as the recommended dose for patients with RLS, however, study XP083 did not include a 600 mg dose arm and a postmarketing requirement was imposed to study the effects of driving associated with the 600 mg dose of GEN.

The findings of study XP083 resulted in the statement in the Warnings and Precautions section in labeling “*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.*” In addition, the Agency required the sponsor (Glaxo Group, Ltd.) to study the 600 mg dose of Horizant in a simulated driving study as a Post-Marketing Requirement (PMR).

**1588-7** A simulated driving trial in healthy adult subjects treated with 600 mg gabapentin enacarbil that includes active comparator and placebo arms.

The timetable you submitted on March 28, 2011 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 05/2011  
Study Completion: 10/2011  
Final Report Submission: 02/2012

The Division and the Sponsor GSK held an informal teleconference on May 24, 2011 from 12:00-1:00 PM to discuss the design of the Driving Study for the 600 mg dose. The Division described three priorities for the 600 mg Horizant driving study: 1) to study the duration of the effect Horizant has on driving throughout the day, 2) study the duration of the effect Horizant has on driving over days to weeks. The Division expressed their concern that patients cannot rely on their own sense of somnolence to make judgments about their ability drive safely. In addition, high plasma levels did not appear to predict poor driving performance.

The Division and the Sponsor wished to complete driving study at the 600 mg as rapidly as possible to obtain the information quickly. The company proposed conducting the trial in healthy volunteers to expedite completion of the trial and the Sponsor proposed shortening the trial duration to approximately 5-7 days on treatment.

The Division response stressed the importance of obtaining information concerning the duration of the effect on driving over weeks. The Division recommended the Sponsor study individuals who had impaired driving on Horizant on Day-6 and continue to treat and follow the effect on driving for an additional 2-4 weeks. The Sponsor asked if they could enroll healthy volunteers to expedite enrollment. The Division indicated there could be differences in response to drug between healthy volunteers and patients with RLS but agreed to allow the company to enroll healthy subjects to expedite completion of the study.

Glaxo submitted the completed study report for trial RXP114111 that examined the effects of GEN 600 mg on simulated driving performance compared to placebo and diphenhydramine (DPH) functioning as an active control, in healthy subjects. The results of study RXP114111 are considered in the context of the previous driving studies, the updated safety information in patients with post-herpetic neuralgia (PHN), postmarketing and published information submitted by GSK. The review also determines if the study fulfills the conditions of the PMR.

This review also addresses labeling supplement #6, a Changes Being Effected (CBE) supplement requested by the agency to add increased creatine kinase to the postmarketing adverse events section in all gabapentin-containing products. Labeling Supplement#7 includes labeling changes that describe information from an in vitro ethanol dissolution study that address PMR 1588-6, to assess Horizant 600 mg tablets for potential alcohol related dose dumping.

GSK also include final study report for study RXP115720 (supplement #7) designed to fulfill PMR 1588-10 to conduct a study Drug-Drug interaction (PK and PD) of morphine administered with GEN in

this submission. The Sponsor also submitted revised label language regarding the potential DDI between morphine and GEN.

## **2. Background**

The results of a previously submitted parallel-group study (XP083) indicated that patients with RLS, experienced impairments in simulated driving ability at GEN doses of 1200 and 1800 mg taken once daily for 2 weeks. The degree of impairment was similar to that following a single dose of 50 mg diphenhydramine (DPH) administered as an active control to demonstrate assay sensitivity.

The decision to study healthy subjects was based on the results of an earlier simulated driving study (XP088) that compared driving performance between healthy subjects and untreated adult subjects with RLS. In general, the pattern of AEs and the pharmacokinetic (PK) parameters for GEN are similar between these two populations. However, the conclusion that driving performance was similar was primarily based on the comparison of changes in Lane Position Variation (LPV) between healthy subjects and patients with RLS. Although, the study demonstrated no significant differences for the comparison of LPV, RLS patients had increased levels of somnolence and an increased number of crashes compared to healthy subjects.

## **3. CMC/Device**

The submission did not contain new CMC information.

## **4. Nonclinical Pharmacology/Toxicology**

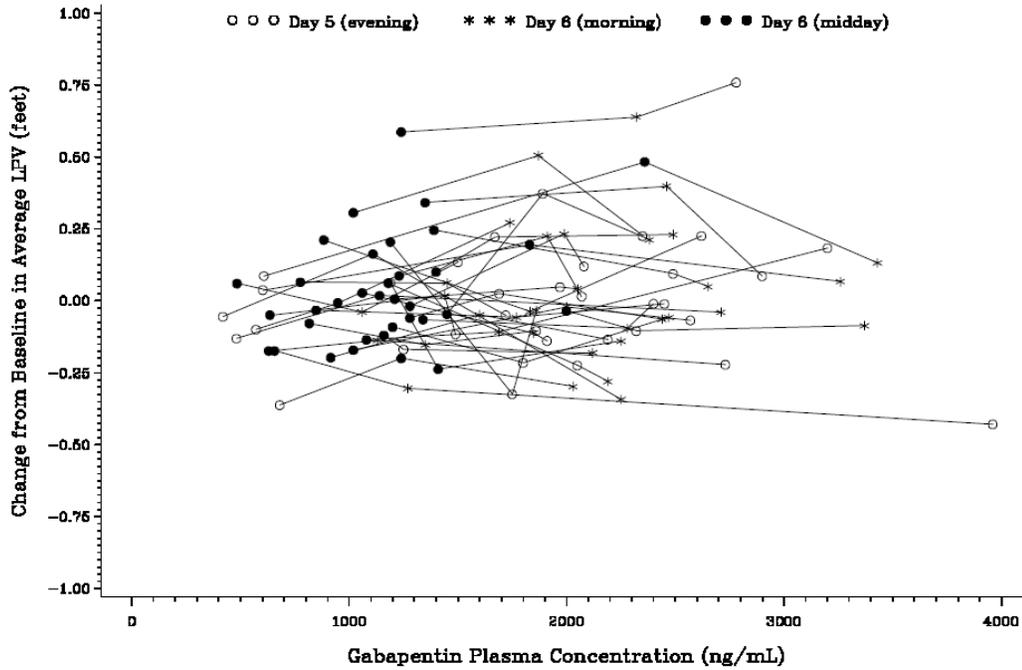
The submission did not contain new Pharmacology/Toxicology information.

## **5. Clinical Pharmacology/Biopharmaceutics**

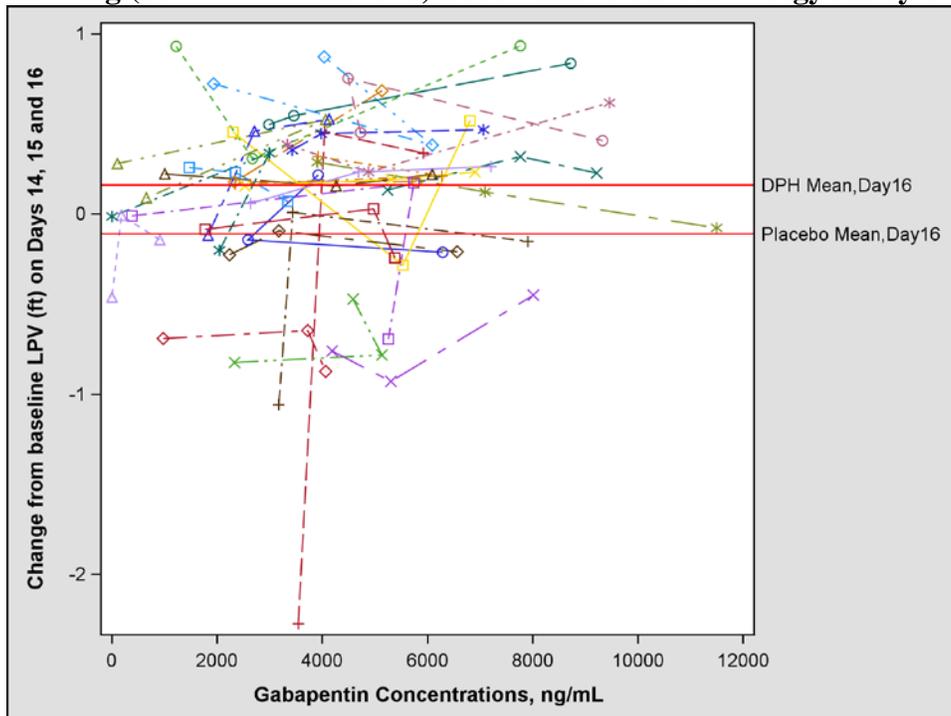
The Sponsor's analysis of the change from baseline in LPV as a function of the plasma gabapentin levels found no relationship between plasma concentrations and LPV in subjects taking Horizant 600 mg, in study RXP114111. The Office of Clinical Pharmacology conducted an independent analysis to explore the relationship between change from baseline in LPV and plasma gabapentin levels Horizant 600 mg in study RXP114111 and 1200 mg and 1800 mg tested in study XP083 and found no relationship between the two parameters.

Dr. Bhattaram (Clinical Pharmacology Reviewer) and Dr. Goldstein (Clinical Reviewer) independently examined plasma concentrations in subjects who experienced single and those who experienced multiple crashes and found no relation between crashes and plasma concentration. There was also no apparent relationship between Speed Variability and plasma gabapentin levels in study RXP 114111 (healthy subjects) or XP083 (RLS patients).

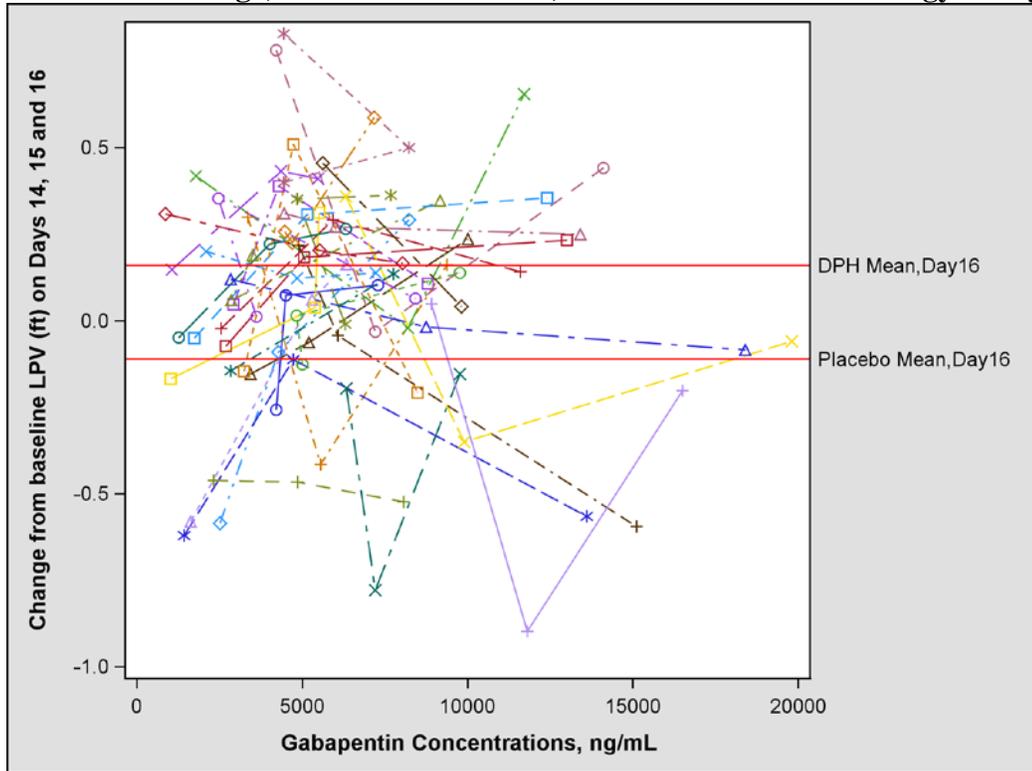
**Fig 1: Study RXP114111-Exploration for Lane Position Variability/Plasma Concentration Relationship 600 mg (Previous Submission) Sponsor's Analysis**



**Fig 2: Study XP083-Exploration for Lane Position Variability/Plasma Concentration Relationship 1200 mg (Previous Submission) FDA Clinical Pharmacology Analysis**



**Fig 3: XP-083-Exploration for Lane Position Variability/Plasma Concentration Relationship  
Horizant 2400 mg (Previous Submission) FDA Clinical Pharmacology Analysis**



**Morphine GEn Drug Interaction Study Submission in Response to PMR  
1588-101588-10**

At the time of approval, GSK was required to study the effects of:

*A clinical drug-drug interaction trial to evaluate the pharmacokinetic and the pharmacodynamic interaction between gabapentin enacarbil and morphine.*

*The timetable you submitted on April 1, 2011 states that you will conduct this study according to the following schedule:*

*Final Protocol Submission: 07/2011  
Trial Completion: 12/2011  
Final Report Submission: 04/2012*

*Submit draft protocols in advance to allow for comments by the Division prior to final protocol submission.*

The PMR was required because of a published report of by Eckhardt (2000) describing an increase in pain tolerance along with a 44% increase in gabapentin exposure (AUC) in male subjects given oral morphine and gabapentin. Complaints of somnolence, dizziness, and nausea were more frequent in with morphine and gabapentin compared to morphine alone.

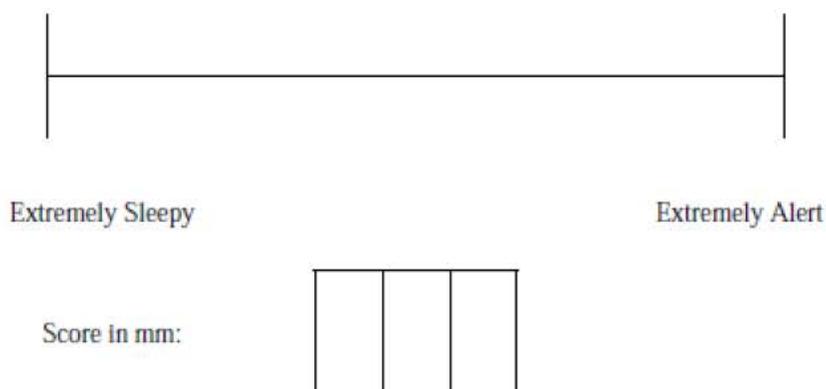
The Division of Clinical Pharmacology reviewed results from the Sponsor’s completed DDI study. The review indicates there is no PK interaction between Morphine and GEN. The combination of GEN and Morphine was associated with an increase in somnolence, dizziness and nausea compared to administration of either drug alone. There is an increased risk for somnolence/sedation following administration of morphine and GEN. The increasing risk for somnolence peaks at approximately 8 hours after dosing with GEN and morphine. Clinical pharmacology recommended changes to the Sponsor’s language regarding the risk for somnolence in addition, The Division of Clinical Pharmacology considers the PMR fulfilled. The review contained recommended changes to the label that appear at the Labeling Section of this review.

**Table 1: Morphine Drug Interaction Study PK Results (Clinical Pharmacology Table)**

Parameter	Ratio (Combination/Alone) (90% CI)		
	GEN	Morphine	Morphine-6-glucuronide
AUC <sub>t</sub> (ng.h/ml)	1.10 (1.03-1.16)	1.06 (1.1-1.09)	0.99 (0.92-1.05)
C <sub>max</sub> (ng/ml)	1.02 (0.92-1.12)	1.05 (0.97-1.13)	0.95 (0.85-1.06)

**Fig 4: Visual Analogue for Sedation**

How alert do you feel?



**Table 2: Mean (SE) Somnolence/Sedation VAS over time (Sponsor's Table)**

Protocol: RXP115720  
Population: Pharmacodynamic

Page 1 of 3

Table 12.1  
Summary of Visual Analog Scale (VAS) Scores (mm)

Symptom	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Somnolence/Sedation	Morphine placebo + GEN 600 mg	16	Baseline	16	71.9	26.82	80.5	18	100
			2 H	16	83.2	18.79	94.5	48	99
			4 H	16	71.5	25.94	81.5	29	99
			6 H	16	72.8	21.83	75.0	38	99
			8 H	16	74.4	21.45	79.0	36	99
			10 H	16	75.4	21.08	78.5	33	99
	Morphine ER 60 mg + GEN placebo	15	Baseline	15	80.1	16.87	82.0	49	99
			2 H	15	84.8	13.98	87.0	49	99
			4 H	15	65.7	28.38	71.0	10	99
			6 H	15	75.4	16.56	79.0	47	99
			8 H	15	74.4	22.14	83.0	34	100
			10 H	15	72.8	17.93	77.0	49	99
	Morphine ER 60 mg + GEN 600 mg	18	Baseline	18	69.4	26.02	77.0	20	99
			2 H	18	75.2	21.20	77.5	27	99
			4 H	18	61.8	28.99	70.5	5	99
6 H			18	66.4	28.49	75.0	6	99	
8 H			18	57.6	30.89	62.5	2	99	
10 H			18	61.8	27.06	60.5	4	99	

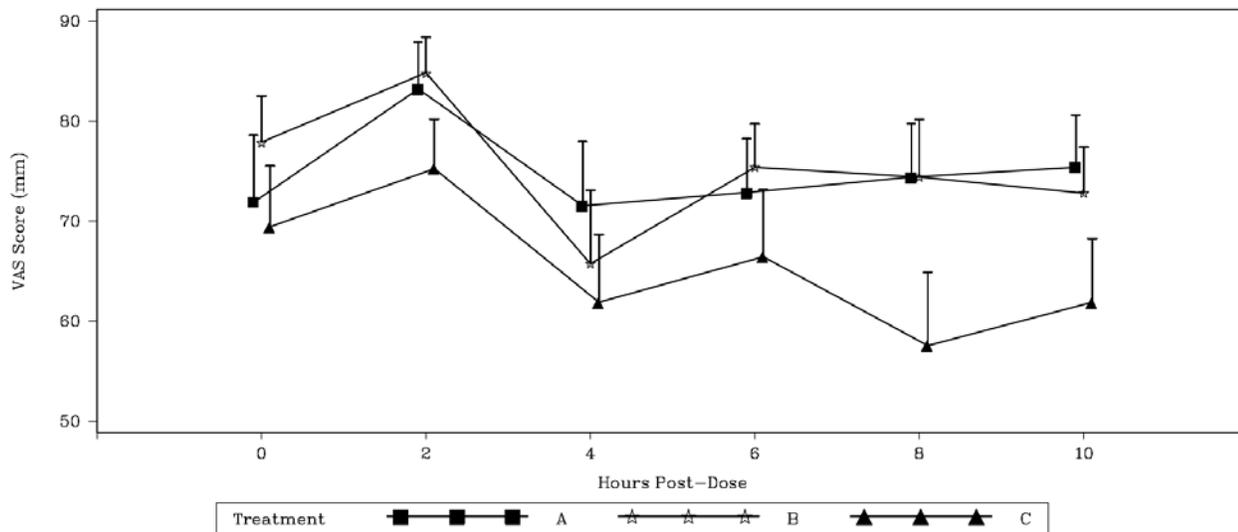
Lower VAS score = Less Awake

CONFIDENTIAL

2011N124968\_00  
RXP115720

Note: The Somnolence/Sedation VAS was a scale from 'Extremely Sleepy' to 'Extremely Alert', with higher scores indicating more alertness/less sleepiness. The Dizziness VAS was a scale from 'Not Dizzy' to 'Extremely Dizzy', with higher scores indicating more dizziness. The Nausea VAS was a scale from 'Not Nauseous' to 'Nauseous', with higher scores indicating more nausea.  
\\ausbt1\ausbt101\GSK GSK115720\Rev Final TLF\TLF\T1201.SAS 22DEC2011 11:18

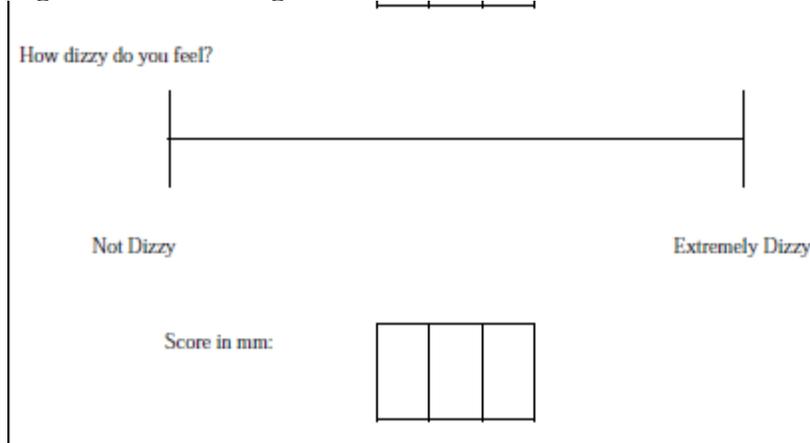
**Fig5: Time course of Somnolence following GEN, Morphine or GEN+Morphine**



**CDTL Comment**

Somnolence measured on the VAS (reported and decreased alertness) is worse following dosing with the combination of GEn and Morphine compared to either drug alone. The effect seemed to be the greatest between 6 to 10 hours following dosing.

**Fig 6: Visual Analogue for Dizziness**



**Table 3: Dizziness VAS Rating**

Protocol: RXP115720  
Population: Pharmacodynamic

Table 12.1  
Summary of Visual Analog Scale (VAS) Scores (mm)

Symptom	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Dizziness	Morphine placebo + GEn 600 mg	16	Baseline	16	4.8	7.74	2.0	1	30
			2 H	16	2.8	1.69	2.0	1	5
			4 H	16	8.1	13.12	2.5	1	53
			6 H	16	9.1	15.18	3.0	1	62
			8 H	16	7.4	12.64	2.5	1	51
			10 H	16	7.2	14.64	3.0	1	61
	Morphine ER 60 mg + GEn placebo	15	Baseline	15	2.5	2.95	1.0	0	11
			2 H	15	3.9	4.50	2.0	1	15
			4 H	15	5.3	5.69	2.0	1	20
			6 H	15	8.2	12.81	3.0	1	51
			8 H	15	8.9	18.95	2.0	0	75
	Morphine ER 60 mg + GEn 600 mg	18	Baseline	18	3.3	2.56	2.5	0	8
			2 H	18	7.3	16.01	2.0	0	70
			4 H	18	8.8	15.35	3.0	0	66
			6 H	18	11.7	19.30	3.5	0	73
8 H			18	14.8	23.57	4.0	1	98	
10 H	18	12.6	22.56	4.5	1	98			

Higher VAS score = greater feeling of Dizziness

Note: The Somnolence/Sedation VAS was a scale from 'Extremely Sleepy' to 'Extremely Alert', with higher scores indicating more alertness/less sleepiness. The Dizziness VAS was a scale from 'Not Dizzy' to 'Extremely Dizzy', with higher scores indicating more dizziness. The Nausea VAS was a scale from 'Not Nauseous' to 'Nauseous', with higher scores indicating more nausea.  
\\ausbt1\ausbt101\GSK GSK115720\Rev Final TLF\TLF\T1201.SAS 22DEC2011 11:18

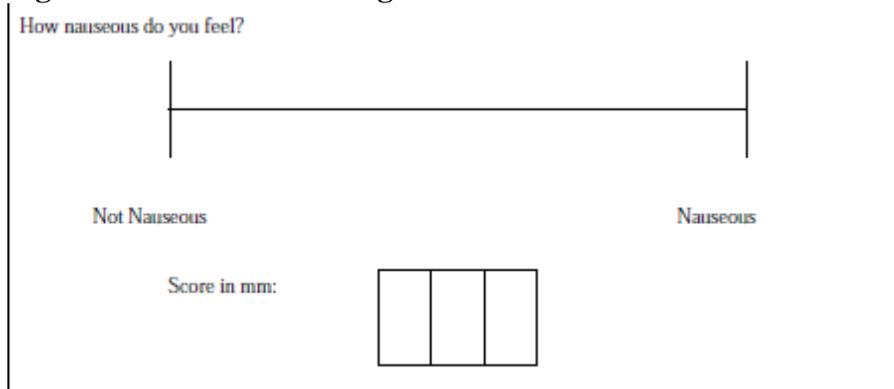
CONFIDENTIAL

2011N124968.00  
RXP115720

**CDTL Comment**

The mean and extreme values for the dizziness VAS rated by subjects in the study indicate that there is a greater increase in dizziness after receiving the combination of GEN and morphine compared to either drug alone.

**Fig 7: Nausea Visual Analogue Scale**



**Table 4: Nausea VAS Rating (Sponsor Table)**

Protocol: RXP115720  
Population: Pharmacodynamic

Table 12.1  
Summary of Visual Analog Scale (VAS) Scores (mm)

Symptom	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Nausea	Morphine placebo + GEN 600 mg	16	Baseline	16	3.6	4.69	2.0	0	17
			2 H	16	3.1	2.24	2.0	1	8
			4 H	16	4.5	4.55	2.5	1	17
			6 H	16	4.1	3.50	2.5	1	11
			8 H	16	3.7	4.13	2.0	1	17
			10 H	16	3.6	3.84	3.0	0	15
	Morphine ER 60 mg + GEN placebo	15	Baseline	15	1.6	1.72	1.0	0	7
			2 H	15	3.0	2.70	2.0	1	11
			4 H	15	4.4	5.19	2.0	1	20
			6 H	15	4.2	5.05	2.0	1	16
			8 H	15	8.8	18.83	2.0	0	75
			10 H	15	7.7	9.38	3.0	1	33
	Morphine ER 60 mg + GEN 600 mg	18	Baseline	18	2.3	1.50	2.0	1	7
			2 H	18	6.1	12.22	2.5	0	54
			4 H	18	7.6	15.48	2.5	1	66
6 H			18	7.7	15.43	3.0	0	67	
8 H			18	8.2	17.17	2.0	1	71	
10 H			18	8.6	15.78	3.0	1	66	

Higher VAS score = greater feeling of nausea

Note: The Somnolence/Sedation VAS was a scale from 'Extremely Sleepy' to 'Extremely Alert', with higher scores indicating more alertness/less sleepiness. The Dizziness VAS was a scale from 'Not Dizzy' to 'Extremely Dizzy', with higher scores indicating more dizziness. The Nausea VAS was a scale from 'Not Nauseous' to 'Nauseous', with higher scores indicating more nausea.

\\ausbt1\ausbt101\GSK GSK115720\Rev Final TLF\TLF\T1201.SAS 22DEC2011 11:18

**CDTL Comment**

The mean and extreme values for the nausea VAS rated by subjects in the study indicate that there is a greater increase in nausea after receiving the combination of GEN and morphine compared to either drug

alone. The increased severity based on VAS rating of Somnolence, dizziness and nausea are greater when subjects received morphine in combination with GEn compared to either drug given alone. The pharmacodynamic effect should be described in the label (clinical-pharmacology sections) to warn patients about the potential for increased somnolence, dizziness and nausea.

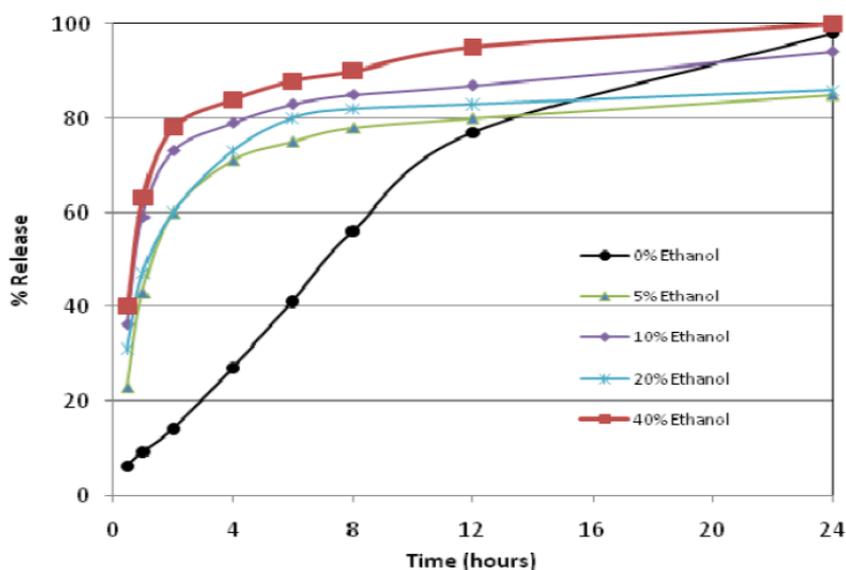
### Ethanol Dissolution Study

The Agency requested an Ethanol Dissolution (Dose Dumping) study of the 600 mg tablet as a PMR at the time of approval. The Office of Clinical Pharmacology reviewed the results of the in vitro study submitted to the Agency on 4/22/11.

**PMR 1588-6 – An in vitro dissolution study to evaluate alcohol dose dumping using the final dissolution method and different concentrations of alcohol up to 40% (0, 5, 10, 20, and 40%).**

**Fig 8: Ethanol Dissolution Study Results**

Dissolution Profile Data for HORIZANT ER Tablets, 600 mg,



As submitted by the Applicant.

Approximately 63% of the total GEn 600 mg tablet was released after 1 hour in 40% ethanol, with the remainder released over the following 23 hours. In the lowest (5%) ethanol concentration, about 43% was released by the end of the first hour.

The Sponsor conducted a simulation designed to model 60% the plasma concentration associated with immediate dose release of GEn ER (Horizant) caused by co-administration with ethanol. The simulation used data from the immediate release (IR) formulation of GEn (not marketed) from Study XP006 and data for extended release formulation (ER, data from Study XP044), combined (in the model not actual) in a 60:40 ratio to create a 600 mg total GEn dose. The predicted concentrations of gabapentin after dosing GEn with the 60:40 IR:ER formulations are within the exposure range of the 600 mg ER tablets.

The sponsor concluded that the rapid release of 60% of the 600 mg tablet of GEN tablet at 1 hour posed no safety concerns.

The Clinical Pharmacology reviewer concluded the intake of alcohol should be restricted when patient take a dose of HORIZANT. The Clinical Pharmacology reviewer suggested that an in vivo alcohol interaction study would be able to define the plasma concentration curve more accurately. However, “*it will not be able to address the safety of driving or its impact on efficacy, i.e. the clinical implication of higher concentration in the first couple hours of dosing when alcohol is taken with HORIZANT. In the event of a negative interaction, the clinical relevance on safety and efficacy will be straight forward.*”

**The sponsor has fulfilled PMR 1588-6** – *An in vitro dissolution study to evaluate alcohol dose dumping using the final dissolution method and different concentrations of alcohol up to 40% (0, 5, 10, 20, and 40%).*

### **CDTL Comment**

The GEN immediate release is not an approved product and the clinical effects that immediate release GEN has on patients with RLS even without co-administered ethanol are unknown. The comparison of a 60:40 GEN IR to ER ratio does not provide sufficient information to base inference concerning how reliably the proposed simulation mimics the effects of dose dumping in ethanol. I agree with the office of Clinical Pharmacology reviewer’s opinion that the dissolution information does not inform how the effect of ethanol related dose dumping would influence the clinical safety profile of Horizant. The sponsor did not present in vivo data from studies that compared the risk for adverse reactions caused by taking GEN (immediate release) with ethanol compared to taking GEN. It also appears that gabapentin plasma levels do not predict adverse effects on simulated driving. The predicted Cmax associated with taking GEN occurs 2 hours earlier when given with 40% ethanol. Usually GEN Tmax occurs around 10-12 PM, 5-7 hours after taking Horizant at 5 PM as recommended. The sponsor’s model predicts the Tmax in the presence of 40% ethanol would occur 2 hours after taking Horizant or at approximately 7 PM. The finding increases concern that adverse reactions may occur much earlier in patients who take alcohol and GEN at nearly the same time. The PMR is fulfilled.

## **6. Clinical Microbiology**

There was no new Clinical Microbiology information contained in this submission

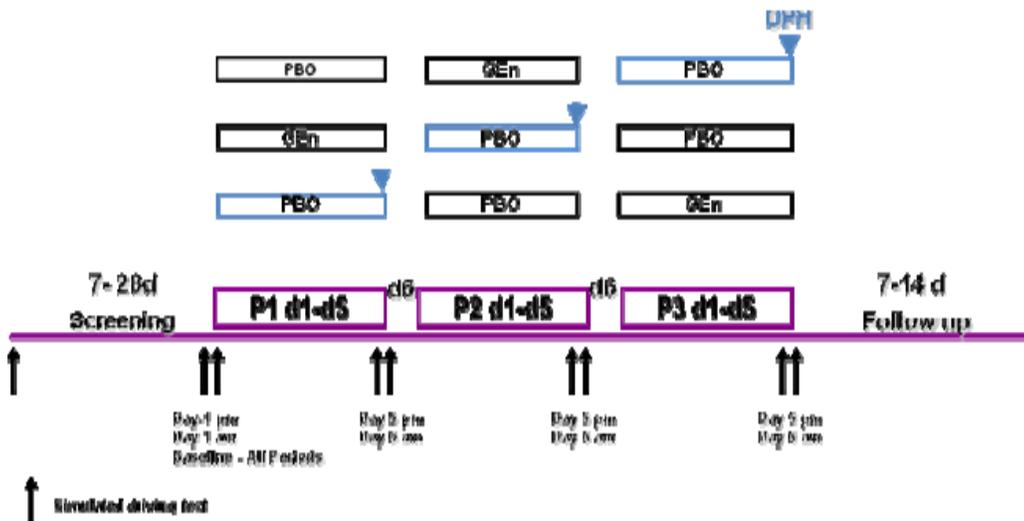
## **7. Clinical-Simulated Driving Study**

### ***Description Study RXP114111***

RXP114111 was a randomized, double-blind, double-dummy, active- and placebo-controlled, 3-period crossover study designed to assess the effect of gabapentin enacarbil (GEN) 600 mg on simulated driving performance in healthy adult subjects.

## Study Design

**Fig: 9**  
**Trial Design Schematic**



Thirty-six healthy male and female adult subjects (mean age 36.6) enrolled in the study. The total duration of the subject's participation in the study was up to approximately 9 weeks, which included up to a 28-day Screening Period, three 6-day Treatment Periods, 2 additional washout days, and an approximately 14-day Follow-up Period.

Simulated driving tests were conducted at baseline prior to the start of dosing (Day -1 in the evening between 7 and 9 pm and Day 1 in the morning between 7 and 9 AM and between 11am and 1pm), on Day 5 of each treatment period in the evening (7-9 pm) and on Day 6 of each treatment period in the morning (7-9 am) and midday (between 11am and 1pm).

The Tmax of GEn ER occurs approximately 7 hours after dosing with food. The recommended dosing time is 5 PM, Tmax should generally occur late in the evening when patients would generally not drive. For this study, simulated driving assessments were conducted approximately 2 to 4 hours after dosing on Day 5 (7 to 9 PM) and on the following morning (7 to 9 AM, approximately 14 to 16 hours after dosing) and at midday (11 AM to 1 PM, approximately 18 to 20 hours after dosing) on Day 6 of each treatment period. Simulated driving was not assessed near the Tmax of GEn however, simulated driving was assessed near the Tmax in all patients following a single dose of 50 mg of diphenhydramine.

Subjects received all three treatments in a randomized sequence: placebo, GEn 600 mg, and DPH 50 mg. Each treatment period consisted of 6 days, with subjects dosed at approximately 5 PM on each dosing day. All subjects received the following treatments in random sequence:

A. Placebo

- GEn matching placebo + DPH matching placebo on Days 1 through 5
- GEn matching placebo + DPH matching placebo on Day 6

B. GEn 600 mg

- GEn 600 mg + DPH matching placebo on Days 1 through 5
- GEn matching placebo + DPH matching placebo on Day 6

C. DPH 50 mg

- GEn matching placebo + DPH matching placebo on Days 1 through 4
- GEn matching placebo + DPH 50 mg on Day 5
- GEn matching placebo + DPH matching placebo on Day 6

Simulated driving evaluations were conducted at:

- **Baseline (on Day -1)** before the start of dosing in the evening between 7 and 9 PM
- **Day 1** in the morning between 7 and 9 AM, and at midday between 11 AM and 1 PM)
- **Day 5** of each treatment period in the evening (7 to 9 PM)
- **Day 6** of each treatment period in the **morning** (7 to 9 AM) and at **midday** (11 AM to 1 PM).

These time points were selected because they represent times when subjects are likely to be driving (i.e., close to the times of morning and evening commuting periods) in relation to taking Horizant. In addition, in this present study, a midday simulated driving test was conducted to assess the persistence of any driving impairment into the morning after taking Horizant.

After a 5-minute practice drive, each subject completed a 60-minute simulated driving test. The simulated driving test consisted of a 2-lane rural highway with gradual curves and oncoming vehicles approximately every 10 minutes. Subjects were instructed to maintain a speed of 55 mph throughout the simulated driving test. Study center personnel monitored all subjects throughout the simulated driving test by watching the computerized display of the roadway and driving simulator performance. All subjects participated in PK, pharmacodynamic, and safety assessments. All Baseline (pre-treatment) simulated driving evaluations were completed first (Evening, Morning and Midday) that provided subjects with the maximum amount of practice before starting the treatment portion of the study.

To ensure adequate washout of DPH before administration of study drug in the next dosing period, placebo was administered on Day 6 of Treatment Periods 1 and 2, as stated in the protocol. However, the sponsor reported, the study center erroneously included an additional drug-free day between Treatment Periods 1 and 2 and between Treatment Periods 2 and 3 for all subjects. The protocol violation lowers the risk for carry-over medications effects related to DPH (active control) influencing the results treatment in the period that follows (placebo or GEn) and the protocol violation did not appear to bias the results of subsequent driving evaluations.

## Patient Demographics Disposition

**Table 5**

**Table 3 Summary of Subject Disposition and Demographic Characteristics**

	Overall N=36
<b>Number of Subjects</b>	
Number of subjects completed, n (%)	35 (97)
Number of subjects discontinued, n (%)	1 (3)
Reasons for discontinuation, n (%)	
Adverse event	1 (3)
Number of subjects in PK Population, n (%)	35 (97)
Number of subjects in ITT Population, n (%)	36 (100)
Number of subjects in Safety Population, n (%)	36 (100)
<b>Demographics</b>	
Age (years), Mean (SD)	36.6 (11.75)
Sex, n (%)	
Female	16 (44)
Male	20 (56)
Height (cm), Mean (SD)	167.36 (7.375)
Weight (kg), Mean (SD)	72.20 (11.438)
Body Mass Index (kg/m <sup>2</sup> ), Mean (SD)	25.67 (2.874)
Ethnicity, n (%)	
Hispanic or Latino	21 (58)
Not Hispanic or Latino	15 (42)
Race, n (%)	
African American/African Heritage	9 (25)
Asian - Japanese Heritage	1 (3)
White - White/Caucasian/European Heritage	25 (69)
White and African American/African Heritage	1 (3)

Data Source: Table 9.1, Table 9.3, Table 9.4, and Table 9.5  
 ITT=Intent-to-Treat, PK=pharmacokinetic

The mean age of subjects in study RXP114111 was 36.6 years (range 19-57 years) with n=21 patients below age 40. As Dr. Goldstein points out in her review, the mean age for patients enrolled in the two pivotal clinical trials of GEN in patients with RLS was 49 and 52 years, which is significantly older compared to the healthy subjects in RXP114111. The age difference is important because visual impairments increase with age (50 and older) [MMWR 2004] and LPV increases with age >40 (Perryman et al, 1996). Subjects had visual acuity assessed by the investigator “as being adequate for driving” but there was no justification by the sponsor the results from the much younger study population could be extrapolated to an older RLS population. The differences in mean age between the subjects studied RXP114111 compared to the patients studied in the pivotal RLS trials, raise concerns about making inference to RLS patients taking Horizant based on the results of RXP114111.

## Endpoints

### Primary Endpoint

The primary endpoint was the change from Baseline (Day -1 evening and Day 1 morning and midday, as applicable) to the end of treatment (Day 5 evening and Day 6 morning and midday) in overall lane position variability (LPV).

Lane Position (LP) is measured as the difference in feet between the center of the simulated vehicle and the centerline of the 26-foot wide paved roadway, 13 ft for each lane of travel. When the simulated vehicle crosses over the centerline into oncoming traffic, this difference becomes negative. Lane position (ft) is measured once per second and recorded electronically.  $LP_i$  is the lane position for the “i” th second ( $i=1$  to 3600). The average lane position (ALP) was calculated as:

$$ALP = \frac{\sum_{i=1}^{3600} LP_i}{3600}$$

Lane position variability (in ft) for the 60-minute driving simulation is the standard deviation of  $LP_i$ .  $LPV = LPV$  for the entire 60-minute driving simulation test, then LPV will be computed as  $LPV =$

$$LPV = \left\{ \sum_{i=1}^{3600} (LP_i - ALP)^2 / 3599 \right\}^{1/2}$$

### Secondary Endpoints

- Change from Baseline to the end of treatment in speed variability (SV)
- Number of simulated driving crashes (Days 5 and 6)
- Change from Baseline to the end of treatment in pre-driving alertness visual analogue scale (VAS) score
- Change from Baseline to the end of treatment in post-driving alertness VAS score
- Change from Baseline to the end of treatment in the difference between pre-driving and post-driving alertness VAS scores (pre-driving VAS score change from Baseline – post-driving VAS score change from Baseline)
- Safety and tolerability as measured by incidence of adverse events (AEs) and observed values and changes from Baseline for vital sign parameters and the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Plasma concentrations of gabapentin on completion of each simulated driving test

### Definition of a Crash

A car crash is defined as a collision with an oncoming car, or when the distance to the center line was greater than 18 ft on either side of the road from the center line (through the entire opposite lane of travel). When crashes occur during the simulation, **data collection is suspended while a crash sound effect plays (approximately 2 seconds)**, the vehicle’s speed is set to 0 mph and its position is reset to 6 feet to the right of the roadway centerline. Data collection resumes when control is given back to the driver. Gaps in the data record when the driver does not have control of the car (i.e., following a crash) are not counted as part of the 60-minute simulation period.

## **Results**

### **Sample Size Considerations**

Approximately 36 subjects were planned for enrollment to ensure completion of 30 subjects (i.e., subjects completing all 3-treatment periods). This study was designed to provide an estimate of the difference in mean LPV between active (GEN or DPH) and placebo groups. A sample size of 30 produces a 95% confidence interval (CI) equal to the sample mean plus or minus 0.153 when the estimated standard deviation (SD) is 0.41. This corresponds to the results observed in the XP083 study, where on Day 16 the placebo group had a mean (SD) LPV of 1.26 (0.31) feet and the DPH group had an LPV of 1.52 (0.50) feet, resulting in a 95% CI of (0.10, 0.43) for the treatment difference, i.e., a width of approximately 0.3 ft and an SD of the difference in means of 0.41.

### **CDTL Comment:**

The treatment effect in study RXP-114111 was estimated using the difference in LPV between the placebo and DPH treated groups from study XP-083. However, the difference in treatment effect in XP-083 used LPV an estimate for DPH from a simulated driving assessment performed near the DPH Tmax. This means that study RXP-114111 was adequately powered to demonstrate a treatment effect for DPH for a change in LPV only near Tmax. However, simulated driving was not assessed near Tmax for GEN and the treatment effect (for LPV) is reasonably expected to be smaller at times before and after Tmax. In addition, RXP-114111 was likely underpowered to detect a statistically significant difference for the number of crashes or the number of subjects who crashed, mean SV and perhaps even changes in mean LPV assessed the next day. Lane crossings were not included in the analysis plan although the simulator program recorded the information, but the Sponsor did not include it in the completed study report.

### **Lane Position Variability (LPV)**

The primary endpoint was the change from baseline in LPV on the protocol define testing times shows that there is little difference in LVP between the treatments at any time points except for the DPH group on Day 5. The Day 5 driving assessment was designed to assess the effect on driving caused by DPH when it was near its Tmax. The Tmax of gabapentin after administration of 600 mg of HORIZANT was 5.0 hours in fasted subjects and 7.3 hours in fed subjects as described in labeling. The effect of DPH on the mean and median for LPV was most pronounced on Day 5 (assessed in the evening, near Tmax) however, there was little effect on the Day 6 morning and midday LPV measurements compared to baseline.

The Sponsor performed several analyses of the change from baseline in LPV including an analysis of extreme values and concluded there was no effect of GEN on LPV.

### **CDTL**

These findings suggest, that mean LPV is not sensitive to the effects of medication on driving impairment except when the effect of a drug in this case, DPH the positive control, exerted its maximum effects at Tmax. Other factors such loss of situational awareness, attention span and fatigue may be affected by medications but may not be reflected by changes in mean LPV and these effects may persist well beyond Tmax. In addition, by definition a crash is an extreme deviation in LPV or a crash with the oncoming vehicle in the opposite travel lane but one one passes every 10 minutes. Study RXP114111 did not include a driving evaluation near the Tmax of GEN however, in the previous study XP-083, driving was assessed in patients with RLS taking GEN near Tmax and there was a clear increase in mean LPV that was nearly identical to the increase in mean LPV observed in patients taking DPH and tested near Tmax.

**Table 6: RXP 114111 (Sponsor’s Table) Change in LPV**

**Table 7 Change in Lane Position Variability (ft) (Intent-to-Treat Population)**

Time Point/ Statistic for LPV (ft)	Baseline N=36	Placebo Treatment Period N=36	GEN 600 mg Treatment Period N=35 <sup>a</sup>	DPH 50 mg Treatment Period N=36 <sup>b</sup>
<b>Day 5 PM</b>				
Mean LPV (SD)	1.24 (0.271)	1.24 (0.276)	1.24 (0.320)	1.40 (0.380)
Change from Baseline:				
Adjusted Mean (SE)		-0.01 (0.041)	-0.01 (0.041)	0.16 (0.041)
Trt Diff vs PBO (95% CI)			-0.01 (-0.09, 0.08)	<b>0.17 (0.08, 0.25)</b>
Trt Diff vs DPH (95% CI)			<b>-0.17 (-0.26, -0.09)</b>	
<b>Day 6 AM</b>				
Mean LPV (SD)	1.30 (0.279)	1.34 (0.303)	1.31 (0.324)	1.33 (0.309)
Change from Baseline:				
Adjusted Mean (SE)		0.04 (0.040)	0.01 (0.040)	0.03 (0.040)
Trt Diff vs PBO (95% CI)			-0.03 (-0.11, 0.04)	-0.01 (-0.08, 0.07)
Trt Diff vs DPH (95% CI)			-0.03 (-0.10, 0.04)	
<b>Day 6 Midday</b>				
Mean LPV (SD)	1.24 (0.259)	1.30 (0.300)	1.28 (0.335)	1.30 (0.318)
Change from Baseline:				
Adjusted Mean (SE)		0.06 (0.031)	0.03 (0.031)	0.06 (0.031)
Trt Diff vs PBO (95% CI)			-0.02 (-0.08, 0.03)	0.00 (-0.05, 0.05)
Trt Diff vs DPH (95% CI)			-0.02 (-0.08, 0.03)	

Data Source: Table 12.1 and Table 12.2

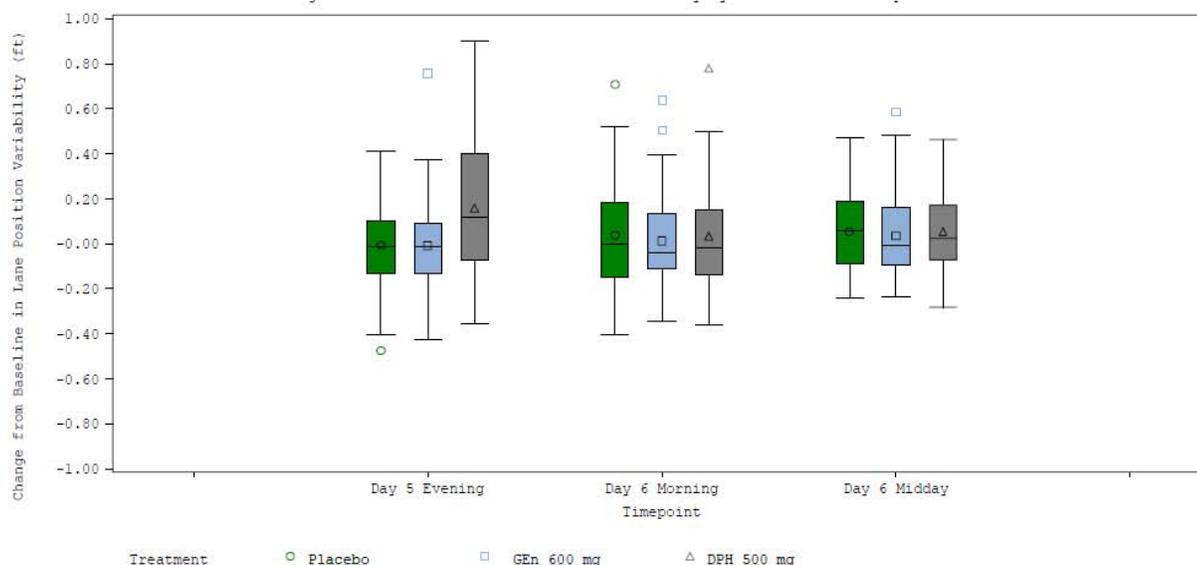
a. N=36 at Baseline.

b. N=35 at Day 5 evening time point.

Note: Bolded cells identify 95% CIs for treatment differences that do not include 0, indicating an apparent difference between the 2 treatments. The analysis method was mixed-model repeated measures with treatment and period as fixed categorical effects, baseline LPV as fixed continuous effect, and subject as a random effect.

CI=confidence interval, Diff=difference, DPH=diphenhydramine, GEN=gabapentin enacarbil, LPV=lane position variability, PBO=placebo, Trt=treatment, vs=versus

**Fig 10: RXP114111 Change from Baseline in Lane Position Variability by Treatment and Time Point (Intent-to-Treat Population) Sponsor’s Figure**



**Speed Variability (SV)**

The Sponsor concluded the effect of GEn on SV was also “not notably different” at any of the tested time-points. However, the Sponsor’s analysis of SV finds there is an increase in SV that corresponds to the periods where the number of crashes and the number of people who experienced crashes. It is unclear if changes in SV are related to how the software program resets following a crash and the need to accelerate to 55 MPH after speed is reset to 0 mph following a crash.

In the Sponsor’s table below, SV was increased when subjects were given DPH and tested as near the Tmax (Day 5 PM) as expected for a positive control. However, it was unexpected to find an increase in the number of crashes and SV in patients who received GEn and DPH on Day 6 at midday. Dr. Goldstein raised the same issue regarding increased SV in relation to crashes in her review and illustrated the point with the table below. The highlighted values in the table below indicate the SV for groups where at least one crash was reported for that time-point. It appears there is threshold effect for mean SV in groups where at least one person experienced a crash regardless of the time-point, at  $SV \geq 1.5$  mph. The increased SV caused subjects to crash or it might be related to some other cause, such as applying the brakes suddenly when subjects realize they are about to crash. For subjects who crashed their SV increased during the same time they experienced a crash in almost all cases. However, the converse is not true; SV had increased at times when crashes did not occur.

The patients in the placebo group for the assessments on Day 6 never return to their baseline SV mean value measured at the same time of day. It suggested that despite the lack of a statistically significant sequence effect driving performance remains worse in the placebo group once patients received GEn or DPH.

**Table 7: INDIVIDUALS WITH CRASHES (Table from Dr. Goldstein)**

SubID	Age	Treatment	Study Day	Timepoint	VAS pre test	VAS post test	Change in LPV	Change in SV	Crashes	Plasma Conc. (ng/mL)
(b) (6)	33	DPH	20	Day 6 Midday	64	33	0.1877	1.1474	1	NA
	36	DPH	13	Day 6 Midday	90	89	0.2547	1.8445	1	NA
	43	DPH	19	Day 5 evening	98	21	0.6832	9.3154	1	NA
	26	DPH	5	Day 5 evening	76	42	0.3276	1.1634	1	NA
	19	DPH	19	Day 5 evening	29	37	0.9003	2.7896	2	NA
		DPH	20	Day 6 Midday	65	64	0.3318	1.5199	1	NA
	19	GEn	20	Day 6 Midday	91	89	-0.046	3.0079	2	1450
	30	GEn	6	Day 6 morning	71	36	-0.037	1.5166	1	1830
	28	GEn	13	Day 6 Midday	66	33	0.3068	1.8269	1	1020
	21	GEn	20	Day 6 Midday	14	35	0.1958	1.7966	1	1830
	28	PBO	13	Day 6 morning	38	1	0.7096	2.0893	1	NA
	48	Baseline	1	Day 1 midday	98	98	NA	NA	1	NA
	21	Baseline	1	Day 1 morning	62	24	NA	NA	1	NA

**Table 8: RXP114111 Change in Speed Variability (Sponsor’s Table)**

**Table 9 Change in Speed Variability (mph) (Intent-to-Treat Population)**

Time Point/ Statistic for SV (mph)	Baseline N=36	Placebo Treatment Period N=36	GEn 600 mg Treatment Period N=35 <sup>a</sup>	DPH 50 mg Treatment Period N=36 <sup>b</sup>
<b>Day 5 PM</b>				
Mean SV (SD)	1.26 (0.905)	1.29 (0.788)	1.46 (1.501)	<b>1.81 (1.791)</b>
Change from Baseline:				
Adjusted Mean (SE)		0.04 (0.227)	0.21 (0.228)	0.60 (0.228)
Trt Diff vs PBO (95% CI)			0.17 (-0.16, 0.49)	<b>0.56 (0.24, 0.89)</b>
Trt Diff vs DPH (95% CI)			<b>-0.40 (-0.72,-0.07)</b>	
<b>Day 6 AM</b>				
Mean SV (SD)	1.31 (0.739)	<b>1.52 (1.000)</b>	<b>1.53 (1.001)</b>	1.44 (0.769)
Change from Baseline:				
Adjusted Mean (SE)		0.21 (0.125)	0.21 (0.126)	0.12 (0.125)
Trt Diff vs PBO (95% CI)			0.00 (-0.29, 0.29)	<b>-0.09 (-0.37, 0.20)</b>
Trt Diff vs DPH (95% CI)			0.09 (-0.20, 0.37)	
<b>Day 6 Midday</b>				
Mean SV (SD)	1.16 (0.573)	1.44 (0.958)	<b>1.59 (1.161)</b>	<b>1.65 (1.374)</b>
Change from Baseline:				
Adjusted Mean (SE)		0.27 (0.169)	0.42 (0.170)	0.49 (0.169)
Trt Diff vs PBO (95% CI)			0.14 (-0.13, 0.42)	0.22 (-0.06, 0.49)
Trt Diff vs DPH (95% CI)			<b>-0.07 (-0.35, 0.20)</b>	

Data Source: [Table 12.4](#) and [Table 12.5](#)

a. N=36 at Baseline.

b. N=35 at Day 5 evening time point.

Note: Bolded cells identify 95% CIs for treatment differences that do not include 0, indicating an apparent difference between the 2 treatments. The analysis method was mixed-model repeated measures with treatment and period as fixed categorical effects, baseline SV as fixed continuous effect, and subject as a random effect.

CI=confidence interval, Diff=difference, DPH=diphenhydramine, GEn=gabapentin enacarbil, PBO=placebo, SV=speed variability, Trt=treatment, vs=versus

### **Number of Simulated Crashes**

The number of patients who experienced simulated crashes increased above baseline levels at two time-periods, in two treatment groups.

**Table 9: Number and Percent of Subjects Who Crashed by Treatment and Evaluation Period**

**Table 10** Number and Percentage of Subjects with Simulated Driving Crashes (Intent-to-Treat Population)

Time Point/ Number of Simulated Driving Crashes	Baseline N=36 n (%)	Placebo Treatment Period N=36 n (%)	GEn 600 mg Treatment Period N=35 <sup>a</sup> n (%)	DPH 50 mg Treatment Period N=36 <sup>b</sup> n (%)
<b>Day 5 PM</b>				
0	36 (100)	36 (100)	35 (100)	32 (91)
1	0	0	0	2 (6)
2	0	0	0	1 (3)
<b>Day 6 AM</b>				
0	34 (94)	35 (97)	34 (97)	36 (100)
1	2 (6)	1 (3)	1 (3)	0
2	0	0	0	0
<b>Day 6 Midday</b>				
0	35 (97)	36 (100)	32 (91)	33 (92)
1	1 (3)	0	2 (6)	3 (8)
2	0	0	1 (3)	0

Data Source: Table 12.6

a. N=36 at Baseline.

b. N=35 at Day 5 evening time point.

DPH=diphenhydramine, GEn=gabapentin enacarbil

**The Sponsor’s Interpretation of Simulated Crashes (p48 of RXP-114111 Study Report)**

*“There were few simulated driving crashes; 12 subjects experienced 16 crashes across 428 simulated 1-hour driving tests. Across the treatment periods, the number of subjects experiencing simulated driving crashes at each time point was small (0 to 3 subjects). There were only 2 subjects who crashed more than once, accounting for 6 of the 16 simulated driving crashes; both subjects experienced 2 simulated crashes in 1 driving test and 1 in another. Simulated driving crashes occurred during both Baseline and on-treatment simulated drives, as well as during all treatment periods. There were 3 subjects who had simulated driving crashes during the Baseline tests (2 during the morning and 1 during the midday time points), suggesting that there is background incidence of simulated driving crashes even in the absence of a drug effect. Evaluation of simulated driving crashes did not show any apparent correlation with other simulated driving endpoints. No obvious patterns indicating a treatment effect were observed in simulated driving crashes.”*

### **CDTL Comment**

The results indicate there were increased crashes on Day 5 in the DPH group tested near Tmax for DPH, as expected. The group that received GEN did not experience an increased number of simulated crashes with moderate gabapentin levels. However, the number of subjects (n=3) who crashed on Day 6 midday in the DPH and GEN groups was identical to the number of subjects who crashed in the DPH group when driving was assessed at the DPH Tmax. Patients treated with GEN and tested on Day 6 midday had the lowest mean gabapentin levels of all the test groups and the mean plasma level of DPH should also be at its lowest level (approaching zero) before driving. The finding suggest plasma concentration is not correlated to the increase number of crashes at the Day 6 midday time point however, regardless of cause, the effect appears equal to the effect of DPH near its Tmax. (active control)

The subjects rated change in the alertness visual analogue scale (VAS) was the lowest on Day 6 midday compared to all other time points, for all treatment groups. This suggests that the subject's perception of alertness (or somnolence) does not predict crashes. It may be that subjects are unable to perceive they are less alert or other factors related to fatigue, or impaired judgment may also play a role in these crashes. A similar lack of awareness of impaired driving impairment was reported in subjects tested while intoxicated with other sedating antihistamines (Verster JC and Volkerts ER 2004).

The fact that the sponsor chose not to assess driving at the Tmax for GEN in study RXP-114111 does not support a conclusion that GEN has no effect on LPV. It is unlikely that the crashes reported Day 6 midday for the groups taking GEN and DPH were caused by chance. The extreme values (outliers) of LPV would also become lost in the large volume of LPV data included when the LPV values were averaged in 10 minute and hourly epochs. Exactly the same number of patients crashed in the DPH group when driving was tested near Tmax (Day 5-evening active control) and on Day 6 midday. If DPH is valid active control and the number of subjects were increased in both drug treated groups but not in the placebo group speaks against chance as the cause the crashes reported on Day 6 midday.

Staner, et al in 2005, reported a similar finding of increased speed variation and an increased crash when simulated driving was assessed the morning after they received a bedtime dose of a sedative hypnotic (zopiclone).

The Sponsor concluded that the increase in crashes was an isolated finding (without an increase in LPV). The conclusion dismisses the finding of increased SV that accompanied the increase in crashes, the increased crashes for DPH on day 5 evening (active control) and on Day 6, midday for DPH and GEN all had an associated increase in mean SV.

The Sponsor argues that driving simulation is not predictive of crashes of "on-road" driving performance. This is true with respect to crashes because the purpose of the driving instructor in a dual controlled vehicle during on-road testing is to avoid collision and injury therefore, crashes do not occur. Direct comparison of the number of on-road crashes and simulated crashes is not ethically possible.

All 36 subjects had 3 separate assessment of baseline (without medication) driving at different timepoints there were 3 subjects who had reported crashes during any of the baseline assessments. However, 36 patients had a single assessment at each different timepoint (n=36 in each group at) on drug. The sponsor's argument that the crashes that occurred at baseline does not consider that all of the baseline assessments were performed first and the assessments on drug occurred after giving subjects on

drug the maximum benefit from a learning effect associated with practice. The practice effect should reduce crashes with repeated simulated driving assessments.

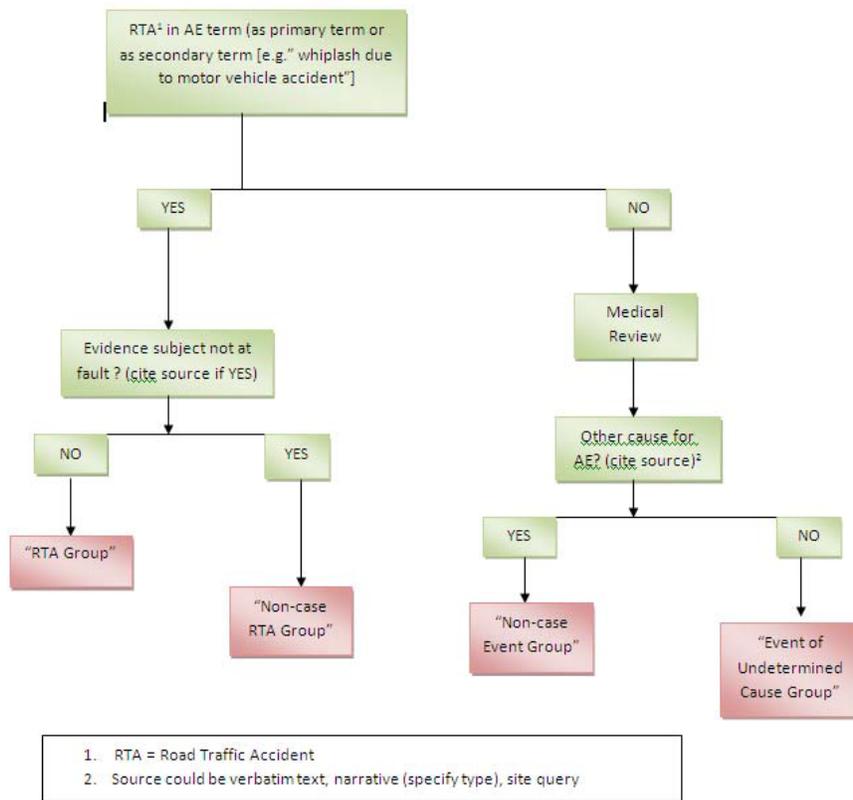
### Clinical Trials Database Search

The Sponsor conducted a clinical trials database search of the adverse event terms from their Phase 2 and 3 clinical trials GEn using the adjudication algorithm below. The list of search terms was extensive for terms describing injury but very few were exclusive to motor vehicle accidents. The Sponsor reported there were 17 events that met their criteria for a road traffic event (RTA), however there were 104 events of undetermined cause.

Passive adverse event reporting is not likely to accurately capture data describing the incidence traffic accidents that occurred during a clinical trial. Traffic accidents related to medication use are likely to be under-reported because an association between the study medication and the accident may go unrecognized by the subject and the study personnel. These medications are not or controlled or illicit substances therefore, they would not raise suspicion at the scene of a RTA that they may have contributed to a driver’s impairment. The quality of the information provided by people involved in a RTA regarding their physical condition and the circumstances leading up to the accident are likely to be affected by an under-reporting bias.

Fig 11

Figure 1 Adjudication Algorithm for Classifying Adverse Events



## Database and Literature Searches for Evidence of Traffic Accidents Associated with Gabapentin Products.

GSK conducted a database search of their own OCEANS (Operating Companies Event Accession and Notification System) global safety database for GEN, an AERS database search and a literature search was conducted for gabapentin products.

The methodology employed for the AERS search as was a “physician agreed upon” list terms based upon the “Accidents and Injuries SMQ” that were associated with injury but were not specific to motor vehicle accident or association with medications. The literature search terms were selected from previously conducted health census and transportation agency listing of motor vehicle accident related terms that was supplemented with terms described as obtained from the internet.

An analysis of post-marketing adverse event data for gabapentin containing products is likely to suffer from the same bias and under-reporting as the clinical trials data. Both methods are unsuitable for determining the incidence of traffic accidents associated with gabapentin containing products.

GSK concluded there were other reasons to discount the results of these analyses that extrapolate a simulated driving experience to real work driving. However, GSK concluded:

*“Based on the post-marketing evaluation described above, the impact of GEN on driving is expected to be no worse than that for gabapentin.”*

GSK also concluded that:

*It is difficult to extrapolate the findings from these 2 studies to an assessment of the real-world risk associated with driving for patients taking GEN because, in the real world, the risk of a driver being involved in a crash depends upon many factors that cannot be directly replicated in a driving simulator e.g. road type (urban versus rural), environmental features, vehicle characteristics, weather, road conditions, traffic density and flow, the behavior of the driver, his or her passenger(s) and other road users, as well as their respective trait (personality) variables.*

### CDTL Comment

Poor road/weather conditions, increased traffic density and driving in an urban setting would likely increase the risk for motor vehicle accident. The simulated driving conditions of the study (description below) were likely to minimize the risk for crashes but perhaps increase the risk for inattention and fatigue. The conditions presented in the driving simulation in study RXP114111 (see below) did not pose situations that challenged driving skills in the ways mentioned by the sponsor. These factors including simulated driving at night, in poor weather condition in dense urban traffic should be considered in future simulated driving studies to approximate closely real-world conditions.

*“After a 5-minute practice drive, each subject completed a 60-minute simulated driving test. The simulated driving test consisted of a 2-lane rural highway with gradual curves and oncoming vehicles approximately every 10 minutes. The subject was instructed to maintain a speed of 55 mph throughout the simulated driving test. Designated study center personnel were required to*

*monitor all subjects throughout the simulated driving test by watching the computerized display of the roadway and driving simulator performance.”*

### **Information from Previous Simulated Driving Study**

**Study XP083:** A Randomized, Double Blind, Active- and Placebo-Controlled, Parallel Group Safety Study Assessing Simulated Driving Performance in XP13512 (GSK1838262) Treated Patients with Restless Legs Syndrome

Study XP083 was a multi-center, randomized, double blind, active- and placebo-controlled, parallel-group study to assess simulated driving performance in XP13512-treated subjects with Restless Legs Syndrome (RLS). Eligible subjects were randomized to receive a once daily dose of placebo (2 groups), XP13512 1200 mg, or XP13512 1800 mg for 16 days. On Day 16 (estimated Tmax), one of the placebo groups also received one 50 mg dose of diphenhydramine (DPH) to assess the effects of an agent known to have sedative properties, while the other 3 groups received a DPH placebo. The primary study objectives were to assess simulated driving performance, cognition, alertness, improvement in symptoms, and safety in XP13512-treated subjects with RLS

The Day 14 evening assessment (2 hours after dosing) corresponding with a relatively low (but increasing) plasma concentration, the Day 16 estimated Tmax assessment with a high (peak) concentration, and the Day 15 simulating a morning driving assessment after 5 PM dose the evening before (lowest plasma concentrations).

#### **Table 10: XP083 Speed Variability (Sponsor’s Table)**

**Table 13 Speed Variability (mph) at Baseline (Day -1 and Day 1), Day 14, Day 15, and Day 16, and Change from Baseline (Day -1 or Day 1) to Day 14, Day 15, and Day 16 in Overall (0 to 60 minutes) Speed Variability (MITT Population)**

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH <sup>a</sup>	95% CI for Mean	ANOVA <sup>b</sup> 95% CI for LS Mean
	N=33 Mean (SD)	N=28 Mean (SD)	N=33 Mean (SD)	N=28 Mean (SD)		
Baseline (Day -1)	2.75 (0.74)	3.45 (1.70)	2.99 (1.05)	3.14 (1.38)		
Baseline (Day 1)	2.59 (0.84)	3.01 (1.24)	2.64 (0.87)	2.96 (1.09)		
Day 14	2.53 (0.96)	3.26 (2.04)	2.67 (0.94)	2.67 (1.26)		
Change from Baseline (Day -1) to Day 14						
Mean (SD)	-0.22 (0.63)	-0.19 (1.42)	-0.32 (1.17)	-0.47 (0.96)		
LS Mean (SE)	-0.24 (0.19)	-0.18 (0.20)	-0.31 (0.19)	-0.46 (0.20)		
XP13512 1200 mg – Pbo					-0.52, 0.58	-0.49, 0.60
XP13512 1800 mg – Pbo					-0.57, 0.36	-0.60, 0.44
Day 15	2.34 (0.80)	3.44 (2.19)	2.58 (0.82)	2.60 (1.09)		
Change from Baseline (Day 1) to Day 15						
Mean (SD)	-0.26 (0.48)	0.43 (2.22)	-0.07 (0.69)	-0.33 (0.43)		
LS Mean (SE)	-0.29 (0.21)	0.44 (0.22)	-0.06 (0.21)	-0.34 (0.23)		
XP13512 1200 mg – Pbo					-0.11, 1.50	0.13, 1.33
XP13512 1800 mg – Pbo					-0.10, 0.49	-0.36, 0.81
Day 16	2.07 (0.65)	3.33 (2.01)	3.23 (2.08)	3.06 (1.54)		
Change from Baseline (Day -1) to Day 16						
Mean	-0.54 (0.55)	-0.12 (2.02)	0.23 (1.95)	-0.08 (1.11)		
LS Mean	-0.57 (0.28)	-0.11 (0.29)	0.24 (0.27)	-0.08 (0.29)		
XP13512 1200 mg – Pbo					-0.35, 1.19	-0.35, 1.26
XP13512 1800 mg – Pbo					0.04, 1.51	0.03, 1.58
Pbo/DPH – Pbo					0.01, 0.92	-0.32, 1.30
XP13512 1200 mg – Pbo/DPH					-0.92, 0.83	
XP13512 1800 mg – Pbo/DPH					-0.52, 1.14	

Data Source: DStable 8.6 and DStable 9.4

a. Pbo/DPH group received diphenhydramine on Day 16 only.

b. Analysis was based on a repeated measures ANOVA model with fixed effects for treatment group, pooled site, visit, and treatment group by visit.

The occasional small increase in speed variability observed for the XP13512 1200 mg at Day 15 and 1800 mg at Day 16 were not reported for other treatments and assessments. The finding of increased SV corresponding to an increase in the number of simulated crashes on Day 15 is very similar to the increase in crashes and SV on Day 6 midday for subjects taking 600 mg of GEN in study RXP114111. The results of study XP-083 were unusual in that the RLS patients who received 1200 mg performed worse than the group that received 1800 mg overall.

**Table 11: XP083 Simulated Crashes by Test Period (Sponsor’s Table)**

**Table 14 Number of Subjects with Simulated Crashes at Baseline and Days 14, 15, and 16 (MITT Population)**

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH <sup>a</sup>
	N=33	N=28	N=33	N=28
<b>Number of Subjects with Crashes, n (%)</b>				
Day -1	3 (9.1)	6 (21.4)	3 (9.1)	2 (7.1)
Day 1	1 (3.1)	4 (14.3)	3 (9.4)	3 (11.1)
Day 14	4 (12.1)	6 (21.4)	1 (3.0)	1 (3.6)
Day 15	1 (3.0)	10 (35.7)	1 (3.2)	0 (0)
Day 16	0 (0)	8 (28.6)	6 (18.2)	3 (10.7)

Data Source: DStable 8.7.1

a. Pbo/DPH group received diphenhydramine on Day 16 only.

Most subjects had only 1 or 3 simulated crashes. One subject in the 1200 mg group and 1 subject in the placebo/DPH group had 4 simulated crashes. One subject each in the 1200 mg and 1800 mg groups experienced 17 (on day 16) and 13 (also on day 16) simulated crashes, respectively. On day 14, 10 patients had crashes, one patient in the 1200 mg group had 13 crashes on day 15

At the Day 15 AM assessment, a total of 10 subjects (35.7%) in the 1200 mg group experienced simulated crashes, an increase from 4 subjects (14.3%) at Baseline (Day 1). Seven of them had 1 to 2 simulated crashes, 2 subjects had 4 crashes, and 1 subject had 13 simulated crashes. The placebo and 1800 mg group each had 1 subject with 1 simulated crash. No subjects had simulated crashes in the placebo/DPH group since they received placebo on day 15 and DPH on day 16.

The Sponsor's Conclusions from Study XP083 CSR p128

*“Based on the assessment of driving performance in the study, it appears that XP13512 administration to RLS patients has a similar effect on driving performance to a 50 mg dose of diphenhydramine.*

**XP088 Study Report.**

The sponsor noted in the Study XP-088 study report that changes in SV and increased crashes have been noted in during simulated in patients with other sleep disorders specifically sleep apnea.

*“Driving ability has been assessed using this driving simulation approach in subjects with sleep apnea compared with normal subjects [Risser, 2000]. The study showed that sleep apnea subjects had more lane position variability than normal controls. In addition, the lane position variability increased over time. The sleep apnea group also had significantly greater variability in speed and increased crash frequency than the control group. These changes are in agreement with the findings from studies using various types of driving simulators [Findley, 1989; Haraldsson, 1990].”*

Study XP-088 compared simulated driving performance in patients with RLS to healthy subjects. The Sponsor's discussion of the study results and conclusion indicate that there are differences in simulated driving performance between patients with RLS and healthy subjects.

*“RLS subjects were similar to normal subjects with regard to lane position variability, speed variability, and brake reaction time during both driving simulator tests. For speed variability by epoch comparing groups, it is noted that there was increased variability for three RLS subjects seen in the later epochs for the Day 2 (AM) drive. RLS subjects also had twice as many crashes than normal subjects (4 crashes vs. 2 crashes), although the number of subjects who experienced crashes was the same for both groups.”*

*“The timing of the crashes coincided with the augmentation of speed variability and, to some extent, lane position variability, in both populations. Two of the 3 RLS subjects whose speed variability deteriorated during the last 2 epochs experienced crashes at the same time. The worsening of driving performance in the later epochs of the test observed in these RLS individuals is typically seen in subjects with sleep disorders or sleep deprivation [Risser, 2000; Ware, 2006; May, 2005] and suggests that sleep disturbance caused by RLS may affect driving performance in selected subjects whose psychomotor function may be more prone to sleep deprivation.” Therefore, there is reason to believe that patients with RLS may have a different degree of driving impairment than healthy volunteers.”*

## ***Adverse Event reports of Somnolence and Population Differences by Indication***

As Dr. Goldstein points out in her review, the percentage of patients reporting somnolence as an AE taking 600 mg of Horizant in the RLS pivotal trial (20%) was higher than the percentage of patients reporting somnolence in the postherpetic neuralgia (PHN) treated with 1200 mg (8%), 2400 mg (11%) or 3600 mg (14%). In addition, the median age of patients in the postherpetic neuralgia (64 years) trials were 10-15 years older than the median age of patients in the pivotal trial in RLS (XP052=52 years, XP053=49 years). The finding that older patients treated for postherpetic neuralgia with substantially higher doses of Horizant reported less somnolence is biologically implausible. The finding suggests that patients treated with Horizant for RLS are more susceptible to somnolence compared to patients with other illnesses and possibly healthy subjects. This finding raises doubt about the Sponsor's assumption that information from healthy subjects treated with Horizant can support reliable inference concerning somnolence and simulated driving performance in patients with RLS.

### **Table 12: Somnolence in Controlled Trials of RLS (from the approved label)**

**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 <sup>a</sup> (N = 245) %	HORIZANT 600 mg/day <sup>b</sup> (N = 163) %	HORIZANT 1,200 mg/day <sup>c</sup> (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

<sup>a</sup> Placebo was a treatment arm in each of the 3 double-blind, placebo-controlled, 12-week clinical trials.

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

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

**Table 13: Somnolence in Controlled Trials of PHN (from the approved label)**

**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**

Body System/Adverse Reaction	Percent of patients			
	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

**Conclusions:**

Although, the comparison of the increased number of crashes reported in studies RXP114111 and XP083 is a cross trial comparison and a comparison of different trial populations (healthy subjects versus patients with RLS), however, the results are similar. The timing of the driving assessments following administration of study medication and the dose of Horizant administered in the two trials were also different. In study RPX114111, number of crashes experienced by healthy subjects on Day-6 midday was greater than the number of crashes in Day 6 morning driving assessment. In study XP-083, patients with RLS had an increased number of crashes at a time that simulates dosing at 5PM and a morning driving assessment the next day. The shift in the increased number of simulated crashed from the morning in XP083 to midday in RPX114111 may be related to the different populations studies in each trial. Patients with RLS may experience fatigue starting earlier in the morning resulting in an increased risk for crashes earlier in the morning) compared to younger healthy subject who experienced increased crashes at Day-6 midday (RXP114111).

There were only small (non-significant) differences in LPV reported in all of the test periods and treatment groups except for DPH tested near Tmax. The clinical meaning of a lack of a significant difference in LPV in a drug associated with increased somnolence and cognitive impairment is uncertain. However, the clinical meaning of an increase in the number of simulated crashes requires less interpretation. The association of increased LPV and simulated crashes comes largely for studies of the acute effects of alcohol on driving. There is far less published information describing the long duration (hangover) effects of sedative drugs on driving performance. Lemon (1993) found subjects had impaired driving performance hours after their blood alcohol returned to 0.0.

The results for simulated driving and cognition for GEN were similar to the active control DPH in study XP083. The number of crashes reported in patients taking 1200 mg of Horizant in study XP083 was

greater than those taking DPH (active control) on day 16 (T max driving assessment) and day 15 (morning after 5 PM dosing driving assessment). In addition, healthy subjects taking Horizant 600 mg in study RXP114111 also reported an increase in the number of simulated crashes the following day (Day 6) at midday. Again, the effect of Horizant 600 mg on simulated crashes appeared similar to the effect of DPH (active) control at Tmax and at Day-6 midday. It suggested that both Horizant 600 mg and the active control both have an effect on simulated driving that occurred later in the (midday) in RXP114111 in healthy volunteers compared to a similar effect observed earlier in the morning in patients with RLS.

The plasma concentration of GEN did not appear to be associated with crashes, LPV or SV. Review of the individual subject data did not demonstrate that subjects who crashed had greater LPV or SV at the time of their highest gabapentin plasma concentration. In the subjects who experienced crashes on GEN none occurred at the highest (measured) gabapentin plasma concentration, most occurred at their mid (of 3 measurements) or lowest plasma level.

### ***Simulated Driving System***

Driving assessments were conducted using a personal computer-based simulation (STISIM Systems Technology, Inc, Hawthorne, CA.) that had separate controls (steering wheel, accelerator and brake pedals). For the simulated driving test, each subject sat in a simulated automobile seat located within a sound- and light-attenuated room. Each subject completed a 5-minute practice drive to allow him or her to become familiar with the simulated environment and the handling characteristics of the simulated automobile. The practice drive consisted of a 2-lane highway environment with several gradual curves and oncoming vehicles that allowed for adaptation to the vehicle's handling and reduced potential learning effects.

After a 5-minute practice drive, each subject completed a 60-minute simulated driving test. The simulated driving test consisted of a 2-lane rural highway with gradual curves and oncoming vehicles approximately every 10 minutes. The subject was instructed to maintain a speed of 55 mph throughout the simulated driving test. Designated study center personnel were required to monitor all subjects throughout the simulated driving test by watching the computerized display of the roadway and driving simulator performance.

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page



## 8. Safety Study RXP114111

As Dr. Goldstein notes in her review, there were, no deaths or nonfatal serious adverse events reported during the study. One subject withdrew prematurely because of a skin abscess that was unrelated to trial participation. Headache was the most frequently reported adverse event during the GEN and DPH segments and it was tied for the most frequently reported adverse event reported in the placebo segments.

### Labeling Supplement #6

#### Changes Being Effected Submitted 6/22/12

#### **Rhabdomyolysis and Elevated Creatine Kinase” associated with Neurontin (gabapentin)**

During routine pharmacovigilance monitoring, the DPV-1 reviewer discovered a number of rhabdomyolysis reports possibly associated with gabapentin use in the Adverse Event Reporting System (AERS). The DVP-1 reviewer and Dr. Sheridan in DNP assessed 13 unique postmarketing cases of rhabdomyolysis and seven cases of elevated creatine kinase (CK) from the AERS database. Of the fourteen cases reporting an indication for gabapentin use, only one used gabapentin for seizures.

Dr. Sheridan (DNP Clinical Reviewer) agreed with the DPV-1 reviewer’s opinion that the evidence for CK elevation is sufficient to recommend adding elevated CK to the gabapentin label in the ADVERSE REACTIONS/POSTMARKETING AND OTHER EXPERIENCE section.

On March 1, 2012, the Division of Neurology Products sent a CBE-30 Supplement Request to GSK requesting a CBE supplement to add “elevated creatine kinase” to the ADVERSE REACTIONS-Postmarketing Experience section of labeling for Neurontin products.

March 20, 2012 This supplemental application, submitted as a "Changes Being Effected in 30 days" supplement, proposes the following change: add "elevated creatine kinase" to the ADVERSE REACTIONS -

Postmarketing Experience section of the package insert now reads:

The following adverse events have been reported in patients receiving gabapentin, in either clinical trials or postmarketing: breast enlargement, and gynecomastia, and elevated creatine kinase. [Added per FDA request for CBE dated March 1, 2012, Reference ID: 3089180]

The CBE-30 will be approved in the action letter for this supplement.

## 1. Advisory Committee Meeting

Not Applicable

## 2. Pediatrics

In the Approval Letter for Horizant (NDA 22399) to GSK dated 04/06/2011 the following Pediatric studies are required Pediatric Research Equity Act (PREA).

We have waived the pediatric study requirement for ages 0 to 12 years because the necessary studies are impossible or impracticable. There are too few patients in this population with clinically significant RLS symptoms for enrollment in a study.

We have deferred submission of your pediatric studies for ages 13 to 16 years for this application until additional safety or effectiveness data have been collected. Adult studies evaluating efficacy with a lower strength dose are necessary before pediatric studies are to begin.

**1588-1** Conduct a PK/PD study in adolescents ages = 13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome.

Final Protocol Submission: 01/2015

Study Completion: 06/2016

Final Report Submission: 06/2017

**1588-2** Conduct a double blind, randomized, placebo-controlled, parallel group efficacy and safety evaluation trial in adolescents = 13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome.

Final Protocol Submission: 06/2015

Study Completion: 10/2023

Final Report Submission: 10/2024

**1588-3** Conduct a long-term safety study of adolescents ages = 13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome. The study must provide a descriptive analysis of

safety data in pediatric patients during at least 12 months of continuous treatment with gabapentin enacarbil at individualized doses in association with the study described in PMR #1588-2.

Final Protocol Submission: 01/2016  
Study Completion: 07/2024  
Final Report Submission: 07/2025

**1588-4** Conduct a driving study in adolescent patients of legal driving age who have Restless Legs Syndrome, using diphenhydramine as active control.

Final Protocol Submission: 06/2017  
Study Completion: 06/2021  
Final Report Submission: 06/2022

Submit draft protocols in advance to allow for comments by the Division prior to final protocol submission.

### **3. Regulatory Issues**

#### **POSTMARKETING REQUIREMENTS UNDER 505(o) (Imposed with the original approval)**

**1588-5** An *in vitro* study to evaluate the potential for gabapentin enacarbil and gabapentin to be inhibitors of CYP2C8 and CYP2B6.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 05/2011  
Study Completion: 08/2011  
Final Report Submission: 10/2011

**Fulfilled Letter sent 4/18/12**

**1588-6** 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%).

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2011  
Study Completion: 04/2011  
Final Report Submission: 06/2011

**Fulfilled addressed in this review**

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient:

- to assess a known serious risk related to adverse effects on patients' ability to drive,
- to identify an unexpected serious risk due to prolongation of the QTc interval in patients taking Horizant,
- to identify an unexpected risk associated with an increased exposure to gabapentin due to a drug interaction with morphine.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

**1588-7** A simulated driving trial in healthy adult subjects treated with 600 mg gabapentin enacarbil that includes active comparator and placebo arms.

The timetable you submitted on March 28, 2011 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 05/2011  
Study Completion: 10/2011  
Final Report Submission: 02/2012

**Fulfilled addressed in this review**

**1588-8** A simulated driving trial in healthy adult subjects treated with an appropriate dose of gabapentin enacarbil determined in PMC 1588-12 that includes active comparator and placebo arms.

The timetable you submitted on March 28, 2011 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 10/2014  
Study Completion: 05/2015  
Final Report Submission: 09/2015

**1588-9** An adequate, randomized, double-blind, placebo- and moxifloxacin-controlled trial to evaluate the effect of gabapentin enacarbil on cardiac repolarization in healthy adult subjects.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2011  
Trial Completion: 05/2012  
Final Report Submission: 11/2012

**1588-11** 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.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2011  
Study/Trial Completion: 06/2011  
Final Report Submission: 06/2011

**Fulfilled letter sent 12/21/11**

**1588-12** Conduct a randomized, placebo-controlled, double blind, parallel-group clinical trial of gabapentin enacarbil at 300 mg/day, 450 mg/day and 600 mg/day in patients with moderate to severe symptoms of RLS.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/2012  
Trial Completion: 07/2014  
Final Report Submission: 02/2015

## **4. Labeling**

### **Agreed Upon Language.**

#### **14.3 Effects on Driving**

Driving performance was assessed in a three-way crossover study in healthy volunteers (mean age 36 years). Subjects were dosed at approximately 5 pm with HORIZANT 600 mg (for five days), diphenhydramine 50 mg (1 dose), and placebo (for five days). After the last dose, driving was evaluated on a computer-based simulation for 1 hour in the evening approximately 2 to 4 hours after dosing (7 to 9 pm), in the morning after dosing (7 to 9 am), and at midday the day after dosing (11 am to 1pm). The primary endpoint of the study was lane position variability. There was no difference in change from baseline in lane position variability for HORIZANT compared to placebo at any of the simulated driving timepoints. Secondary measures included speed variability and the occurrence of simulated crashes. Subjects in this study experienced simulated crashes as described in Table 7. At the times that simulated crashes occurred, there was an increase in average speed variability in the HORIZANT and diphenhydramine treated groups that were most notable in patients who experienced simulated crashes, but no increases in lane position variability. Later time points post-dosing or the effects of driving after more than five days of dosing with HORIZANT were not evaluated.

**Table 14: Simulated Crashes at Evaluated Timepoints (Secondary Measure)**

<b>Simulated Driving Timepoint and Hours Post Dose</b>	<b>Baseline</b> N = 36 n (%)	<b>Placebo</b> N = 36 n (%)	<b>HORIZANT 600 mg</b> N = 35 n (%)	<b>Diphenhydramine 50 mg</b> N = 36 n (%)
<b>Day 5</b> Evening (7 to 9pm) 2 to 4 hours post dose	0 (0)	0 (0)	0 (0)	3 (9)
<b>Day 6</b> Morning (7 to 9am) 14 to 16 hours post dose	2 (6)	1 (3)	1 (3)	0 (0)
<b>Day 6</b> Midday (11am to 1pm) 18 to 20 hours post dose	1 (3)	0 (0)	3 (9)	3 (8)

The results of a separate 2-week driving simulation study in patients (mean age 47 years) with moderate-to-severe primary RLS showed that once daily doses of 1,200 mg and 1,800 mg of HORIZANT significantly impaired simulated driving performance based on lane position variability. An increased number of simulated crashes were reported in patients tested near  $T_{max}$  after receiving 1,200 mg or 1,800 mg of HORIZANT compared to patients treated with diphenhydramine 50 mg. In addition, patients receiving 1,200 mg of HORIZANT experienced an increased number of simulated crashes at 14 to 16 hours after dosing compared with placebo, diphenhydramine, and 1,800 mg of HORIZANT.

The design limitations of these two studies do not permit inference regarding dose response relationship or the duration of the effect HORIZANT has on driving in patients with RLS.

The results of a separate driving simulation study comparing untreated RLS patients and healthy subjects showed no difference in lane position variability but an increase in speed variability associated with a greater number of simulated crashes in RLS patients relative to healthy subjects, which may indicate impaired driving in RLS patients in the absence of medication.

Although, study RXP114111 fulfills the PMR as written, new information from this simulated driving study indicate an increased risk for SV and crashes in healthy subjects after taking 600 mg of Horizant. This increased risk is caused by factors not captured by subject rated measures of perceived somnolence or LPV. The effect of Horizant on the number of crashes is very similar to crashes that occurred on the active control, diphenhydramine. However, the effect on crashes in healthy subjects appears to be delayed compared to the effect in patients with RLS. A comparison of adverse events related to somnolence in the approved Horizant label indicates that RLS patients are also more likely to complain of somnolence compared to older patients treated for post-herpetic neuralgia with substantially higher doses (up to 3600 mg) compared to the recommended 600 mg dose in patients treated for RLS.

In addition, RXP114111 did not address the concerns the Agency has about the duration of the effects on driving that may occur with continued use of Horizant. The Agency still does not know whether patients with RLS will continue to experience an increased risk for crashes and somnolence weeks after starting Horizant 600 mg or if the risk will lessen with continued use and time. The Agency discussed the concern about length of the study with GSK in a teleconference. The Agency believed this

information would be useful to describe in labeling. The Sponsor was aware of the limits of the trial design in providing information concerning the duration of any effect on driving associated with Horizant 600 mg. Their rationale for conducting a short trial was to increase the speed of gathering the information, also an Agency concern.

Information from patients treated with Horizant for postherpetic neuralgia indicates that patients treated for RLS are at greater risk for somnolence even though RLS patients are younger and they received substantially lower doses of Horizant.

- 1) The company has taken the position that the subjects who crashed in Period 3 for GEn and DPH are due to chance. However, the number of individuals who experienced crashes in period 3 on both DPH and GEn were the same as the number of subjects reporting crashes in Period 1 when tested near the Tmax for DPH (active control group).

### **Sponsor's Bulleted Response**

- The relative rates of somnolence/sedation reported by subjects with RLS and healthy subjects is not, in and of itself, sufficient to preclude the acceptability of healthy subjects as a proxy for subjects with RLS in assessments of simulated driving performance as there is a lack of correlation between the reported incidence of somnolence/sedation and impaired driving as assessed in the completed simulated driving studies.

### **CDTL Response**

The sponsor noted in the Study XP-088 study report that changes in SV and increased crashes have been noted in during simulated in patients with other sleep disorders specifically sleep apnea. In addition, the sponsor's comment is not consistent with their own conclusions regarding the results of study XP-088.

*“Driving ability has been assessed using this driving simulation approach in subjects with sleep apnea compared with normal subjects [Risser, 2000]. The study showed that sleep apnea subjects had more lane position variability than normal controls. In addition, the lane position variability increased over time. The sleep apnea group also had significantly greater variability in speed and increased crash frequency than the control group. These changes are in agreement with the findings from studies using various types of driving simulators [Findley, 1989; Haraldsson, 1990].”*

Study XP-088 compared simulated driving performance in patients with RLS to healthy subjects. The sponsor's discussion of the study results and conclusion indicate that there are differences in simulated driving performance between patients with RLS and healthy subjects.

*“RLS subjects were similar to normal subjects with regard to lane position variability, speed variability, and brake reaction time during both driving simulator tests. For speed variability by epoch comparing groups, it is noted that there was increased variability for three RLS subjects seen in the later epochs for the Day 2 (AM) drive. RLS subjects also had twice as many crashes than normal subjects (4 crashes vs. 2 crashes), although the number of subjects who experienced crashes was the same for both groups.”*

*“The timing of the crashes coincided with the augmentation of speed variability and, to some extent, lane position variability, in both populations. Two of the 3 RLS subjects whose speed variability deteriorated during the last 2 epochs experienced crashes at the same time. The worsening of driving performance in the later epochs of the test observed in these RLS individuals is typically seen in subjects with sleep disorders or sleep deprivation [Risser, 2000; Ware, 2006; May, 2005] and suggests that sleep disturbance caused by RLS may affect driving performance in selected subjects whose psychomotor function may be more prone to sleep deprivation.” Therefore, there is reason to believe that patients with RLS may have a different degree of driving impairment than healthy volunteers.”*

- The simulated crashes observed with GEN 600 mg in Study RXP114111 were random events consistent with background incidence and do not constitute a signal of driving impairment.

#### **CDTL Response**

*It is unlikely that the crashes reported Day 6 midday for the groups taking GEN and DPH are caused by chance. The exact same number of patients crashed in the DPH group when driving was tested near Tmax (Day 5 evening active control) and on Day 6 midday. If DPH is considered a valid active control then the fact that the number of subjects who crashed on Day 6 midday were identical for GEN and DPH and no patients in the Placebo group had a reported crash on Day 6 midday which speaks against a chance as a cause the crashes reported on Day 6 midday.*

*Staner, et al in 2005, reported the finding of increased speed variation and increased crashes during simulated driving the morning after bedtime dosing with a sedative hypnotic (zopiclone).*

- The incidence of simulated crashes after treatment with GEN 600 mg in Study RXP114111 was no greater than the background incidence of simulated crashes in all 3 simulated driving studies, and no greater than the background incidence in published simulated driving studies of healthy subjects.

#### **CDTL Response**

*All 36 subjects had 3 separate assessment of baseline (without medication) driving at different timepoints there were 3 subjects who had reported crashes during any of the baseline assessments. Baseline (without medication) assessments in LPV do not change significantly by timepoints<sup>4</sup>. However, 36 patients had a single assessment on each drug at different timepoints following medication dosing. The effect of medications is expected to change with later timepoints. Therefore, 3 patients crashed in 108 baseline driving assessments 2.8% experienced crashes during baseline driving assessments but 3 subjects in 36 driving assessments given GEN (8.3%) crashed during the Day 6 midday driving 1 (3%) on Day 6 morning and 1 (3%) in the placebo group. Three of 36 patients (8.3%) who received DPH also crashed Day 6 midday. The sponsor’s argument that the crashes that occurred at baseline fails to consider that all of the baseline assessments were performed first and the assessments on drug occurred after giving subjects on drug the maximum benefit from a learning effect associated with practice.*

- The baseline incidence of simulated crashes was not different in healthy subjects and subjects with RLS.

**CDTL Comments**

*Comments taken directly from the sponsors XP-088 completed study report stating there was a greater number of crashes in subjects with RLS at baseline in the non-medicated state.*

*Study XP-088 compared simulated driving performance in patients with RLS to healthy subjects. The sponsor’s discussion of the study results and conclusion indicate that there are differences in simulated driving performance between patients with RLS and healthy subjects.*

*“RLS subjects were similar to normal subjects with regard to lane position variability, speed variability, and brake reaction time during both driving simulator tests. For speed variability by epoch comparing groups, it is noted that there was increased variability for three RLS subjects seen in the later epochs for the Day 2 (AM) drive. RLS subjects also had twice as many crashes than normal subjects (4 crashes vs. 2 crashes), although the number of subjects who experienced crashes was the same for both groups.”*

- The timing of simulated crashes in Study RXP114111 did not coincide with maximum drug concentrations of GEN or DPH or the known pharmacodynamics of DPH, indicating a random occurrence unrelated to drug pharmacodynamics.

**CDTL Comment**

*The sponsor did not assess driving performance or conduct PK sampling for the 600 mg dose of GEN near Tmax in study RXP114111. The study reported increased speed variation, deviation from lane boundaries and crashes the next day in subjects who received GEN or DPH. It suggests there are impairments in driving that are not predicted by peak plasma concentration. Poor driving performance (on-road, closed course) was reported in patients tested during an “Alcohol Hangover” by Lemon in 1993.*

- Simulated crashes are not representative of on-road events.

**CDTL Comment**

*The statement by the company is opinion unsupported by data. The company offered no evidence that crashes recorded in a simulator do not forecast an increased risk for on-road crashes.*

- We believe that it is scientifically and procedurally inappropriate and fundamentally unfair to apply different standards to the assessment of driving performance following use of GEN, gabapentin, and other drugs which could be used to treat RLS.

**CDTL Comment**

*The potential effect of dopamine agonist medications on somnolence and driving are described in labeling. It may not be possible to impose a new postmarketing requirement at this time unless new safety information becomes available for these medications.*

(b) (4)

(b) (4)

- The current label for HORIZANT contains a driving warning (“HORIZANT causes significant driving impairment”) that is more severe than other drugs used to treat patients with RLS.

*See CDTL response below*

- Dopamine agonists (ropinirole, pramipexole, rotigotine), which are the most prescribed treatments for RLS, have product labels that report patients falling asleep while driving motor vehicles when taking these agents. It is worth noting that these product labels only instruct that patients should be advised not to drive if they develop sudden onset of sleep and the product is continued.

**CDTL Response**

**WARNINGS AND PRECAUTIONS: Falling Asleep During Activities of Daily Living (From the Approved Mirapex Label Drugs at FDA)**

*“If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), MIRAPEX tablets should ordinarily be discontinued. If a decision is made to continue MIRAPEX tablets, advise patients not to drive and to avoid other potentially dangerous activities. While dose reduction reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.”*

The Horizant label does not advise patients to discontinue Horizant for significant daytime sleepiness. Clearly, the Class label language that is included in all of the labels for dopamine agonists approved for treatment of RLS include a stronger warning.

- Generic gabapentin, prescribed off-label for the treatment of RLS in accordance with RLS treatment guidelines, contains a precaution that instructs prescribers to advise patients that they should not drive a car nor operate other complex machinery until they have gained sufficient experience to gauge any drug effect.

**CDTL Response**

Including such a warning in the gabapentin labels may promote off label use in patients with RLS.

- We are not aware of any initiatives to systematically evaluate driving performance following administration of a dopamine agonist or gabapentin, in the same manner that is being requested for Horizant.

**CDTL Response**

Although these studies for dopamine agonists approved to treat RLS may be requested in the future, it does not dismiss the finding for Horizant

The study to satisfy **PMR 1588-10** to evaluate the pharmacokinetic and the pharmacodynamic interaction between GEN and morphine is also **fulfilled**. I agree with the changes to the product label proposed by the Division of Clinical Pharmacology.

**PMR 1588-6** 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%), is fulfilled.

The label will recommend prescribers advise patients that Horizant should not be administered in the presence of alcohol.

The labeling **supplement (#6)** that adds of “elevated creatine kinase to the postmarketing adverse events section (Section 6) in labeling for all gabapentin containing products **should also be approved.**

**Extension of The Review Cycle**

The Division requested a teleconference with GSK and XenoPort to discuss the results of RXP114111 and the need for a longer duration driving safety study. The T-con was held on December 13, 2012 at 1:00 PM. The Sponsor presented their conclusions concerning the results of study RXP114111 and their response to the Divisions interpretation of the study results. The T-co concluded with an agreement to meet face to face to discuss potential trials design that would provide information that would help establish the duration of the adverse effect Horizant has on the ability to drive. The company submitted a Briefing Package in advance of the face-to-face meeting that included new information and new analyses of the data from study RXP114111. The Briefing Package was substantial and required review therefore, the submission was classified a Major Amendment and the review period was extended by 3 months. The sponsor also responded to an information request from the Division to supply an analysis of the number of times the boundaries of the simulated vehicles crossed the boundaries of the travel lane, each group and for all test periods.

The Briefing Package did not include potential study design elements instead, it simply restated the company’s position regarding the lack of association between crashes during simulated driving and “Real Driving” performance. The Briefing Package also included the Sponsor’s position that vehicle deviation across the lane of travel boundaries are also not evidence of impaired driving. The Sponsor again refers to increased crashes as an isolated finding and refers to the SDLPV as if it is a “Gold Standard” and crashes and increased lane crossings as isolated findings.

**Table 15**

Table 1. Number of Subjects with a Vehicle Edge Out of Lane (LP<2.5 or LP>10.5 feet) and the Total Number of One Second Time Points with a Vehicle Edge Out of Lane.

Treatment	Time of Evaluation	Number (%) of Subjects Out of Lane (LP<0 or LP>13)	Total Number of One Second Time points Out of Lane* (LP<0 or LP>13)
None (baseline) (N = 36)	Day 5 PM	26 (72%)	652
	Day 6 AM	27 (75%)	1001
	Day 6 Midday	26 (72%)	775
Placebo (N = 36)	Day 5 PM	29 (81%)	1031
	Day 6 AM	30 (83%)	1336
	Day 6 Midday	27 (75%)	1218
DPH 50 mg (N = 36)	Day 5 PM	26 (72%)	2240
	Day 6 AM	30 (83%)	1354
	Day 6 Midday	29 (81%)	1447
Gabapentin Enacarbil 600 mg (N = 35)	Day 5 PM	28 (78%)	977
	Day 6 AM	26 (72%)	1688
	Day 6 Midday	26 (72%)	1554

\*Total calculated from summation of all time points and subjects.

Review of the information in the Briefing Package contained graphs in individual driving performance plotting speed variation and lane position for each subject in each study arm. The results of the 3 subjects who crashed on day 6 midday are included below. Although the subjects in the GEN group crashed on day 6 midday, only 1 (subject <sup>(b) (6)</sup>) of the 3 subjects had increased speed or lane crossing during the test period. The finding does not explain the change in mean speed deviation or increase lane in the crossings in the day 6, GEN and DPH test groups but it indicates that they two parameters may not always coincide with increased crashes.



1 Page has been Withheld in Full as b6 immediately following this page

## **LABELING RECOMMENDATIONS**

### **7 DRUG INTERACTIONS**

GEN is released faster from HORIZANT Extended-Release tablets in the presence of alcohol. Consumption of alcohol is not recommended when taking HORIZANT [see *Clinical Pharmacology (12.3)*].

Morphine: HORIZANT taken in conjunction with morphine causes increased somnolence/sedation, dizziness, and nausea when compared with either drug alone [see *Clinical Pharmacology (12.3)*].

### **12 CLINICAL PHARMACOLOGY**

#### **12.3 Pharmacokinetics**

##### ***Drug Interaction:***

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*.

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)

***Ethanol:*** An *in vitro* dissolution study was conducted to evaluate the impact of ethanol (5, 10, 20, and 40%), on the extended-release characteristics of HORIZANT. The *in vitro* study showed that about 63% of the total gabapentin enacarbil dose was released at 1 hour at the highest alcohol level (40%), and about 43% of total drug was released at 1 hour with 5% alcohol. Ethanol causes a more rapid release of gabapentin enacarbil from the extended-release tablets that may increase the risk for adverse events associated with HORIZANT. Consumption of alcohol is not recommended when taking HORIZANT.

***Morphine:*** Administration of a single 600-mg dose of HORIZANT 2 hours after a single 60-mg dose of extended-release morphine sulfate in 18 subjects was associated with increased somnolence/sedation, dizziness, and nausea for the combination compared to HORIZANT or morphine alone as measured by the visual analog scale. No changes in C<sub>max</sub> and AUC of gabapentin, morphine or its active metabolite morphine-6-glucuronide were observed.

**Labeling Supplement #6 CBE (submitted 6/22/12)**

**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, and elevated creatine kinase. [Added per FDA request for CBE dated March 1, 2012, Reference ID: 3089180]

(b) (4)



## 5. Recommendations/Risk Benefit Assessment

**APPROVAL.** Study RXP114111 fulfills the PMR however; the Sponsor's proposed label language required (b) (4) The duration that the adverse effects on simulated driving was not adequately assessed in study RXP114111. The label contains a warning to prescribers about the potential for driving impairment, but it does not describe the duration or if it resolves with continued use.

(b) (4)

(b) (4)

The company is required (PMRs) to study simulated driving performance for lower (effective) doses of Horizant in adults (normal subjects) and in adolescents with RLS under PREA requirements. The design of these studies should follow the Consensus Test Battery for Assessing Impaired Driving Performance developed by U.S. Department of Transportation National Highway Traffic Safety Administration Expert Panel published in March 2011. The study should be performed at a separate, independent facility that is experienced in performing simulated driving tests and interpreting the results. The study should study driving at peak plasma concentration as well the effect throughout the next day. The trial should be of sufficient duration (at least 4 weeks) to determine if the effect on driving improves with continued use of GEN.

## Figure 15

Consensus Protocol | 22

### Appendix A Consensus Test Battery for Assessing Impaired Driving Abilities

#### Alertness/Arousal

- Self-Report: visual analog scales, sleepiness scales
- Laboratory Performance Measures: tests of vigilance
- Sleep Laboratory Measures: physiological measures of sleep onset latency and ability to maintain wakefulness
- Driving Simulator: measures of ability to maintain speed and lane position on a 40+ minute driving scenario

#### Attention and Processing Speed

- Laboratory Performance Measures: tests of working memory, vigilance, focused attention, shifting attention, and divided attention
- Driving Simulator/Instrumented Vehicle: measures of eye movement and gaze, divided attention, and reaction time to crash likely events

#### Reaction Time/Psychomotor Function

- Laboratory Performance Measures: measures of choice/ complex reaction time, upper motor speed and coordination
- Driving Simulator/Instrumented Vehicle: brake reaction time tests, and steering measures (e.g., steering variability)

#### Sensory-Perceptual Function

- Laboratory Performance Measures: tests of visual fields, perimetry testing, and contrast sensitivity testing

#### Executive Function

- Laboratory Performance Measures: tests of mental flexibility, adaptive problem solving, abstract reasoning, impulse control, risk taking/risk assessment, organizational ability (including visuospatial organization), and planning
- Driving Simulator/Instrumented Vehicle: measures of navigational performance

## **REFERENCES**

1. Prevalence of Visual Impairment and Selected Eye Diseases Among Persons Aged >50 Years with and Without Diabetes --- United States, 2002. *MMWR*. 2004 Nov 19; 53(45):1069-1071.
2. Perryman KM, Fitten LJ. *J Geriatr Psychiatry Neurol*. 1996 July; 9(3):136-41.
3. Staner L, Ertlé S., Peter Boeijinga, Rinaudo G, Arnal MA, Muzet A, Luthringer R. Next-day residual effects of hypnotics in DSM-IV primary insomnia: a driving simulator study with simultaneous electroencephalogram monitoring. *Psychopharmacology* (2005) 181: 790–798.
4. Verster JC, Roth T. Standard operation procedures for conducting the on-the-road driving test, and measurement of the standard deviation of lateral position (SDLP). *International Journal of General Medicine*. 2011;4 359–371.
5. Verster JC, Volkerts ER Antihistamines and driving ability: evidence from on-the-road driving studies during normal Traffic Ann Allergy Asthma Immunol. 2004; 92:294–304.
6. National Advanced Driving Simulator (Brown, Dow, Marshall, & Allen, 2007; Salaani, Heydinger, & Grygier, 2006; Senserrick, Brown, Quistberg, Marshall, & Winston, 2007)
7. U.S. Department of Transportation National Highway Traffic Safety Administration, Multiple Medications and Vehicle Crashes: Analysis of Databases, Final Report. May 2008
8. U.S. Department of Transportation National Highway Traffic Safety Administration. Drugs and Human Performance Fact Sheets April 2004.
9. U.S. Department of Transportation National Highway Traffic Safety Administration. Drugged Driving Expert Panel Report: A Consensus Protocol for Assessing the Potential of Drugs to Impair Driving. March 2011.
10. Lemon J. Alcoholic hangover and performance: a review. *Drug and Alcohol Review* (1993) 12, 299-314.

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

GERALD D PODSKALNY  
03/11/2019 02:55:51 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022399Orig1s005**

**MEDICAL REVIEW(S)**

## Review and Evaluation of Clinical Data

---

<b>NDA</b>	<b>22399</b>
<b>Sponsor:</b>	<b>GSK</b>
<b>Drug:</b>	<b>Horizant</b>
<b>Proposed Indication:</b>	<b>RLS</b>
<b>Material Submitted:</b>	<b>Study Report S-005</b>
<b>Correspondence Date:</b>	<b>02/29/2012</b>
<b>Date Received / Agency:</b>	<b>02/29/2012</b>
<b>Date Review Completed:</b>	<b>03/14/2013</b>
<b>Reviewer:</b>	<b>Susanne R. Goldstein, MD Medical Reviewer, DNDP, ODE I</b>

---

### 1. Introduction

Horizant (Gabapentin enacarbil,) was approved on April 6, 2011, for the treatment of moderate to severe Restless Leg Syndrome (RLS). At the time of approval, the Division was concerned that Horizant may cause impairment of driving in patients that persists into the morning after taking Horizant the evening before at 5 PM. The sponsor conducted a simulated driving study, (Study XP-083) in RLS patients taking the 1200 mg and 1800 mg dosages (or placebo). The dose recommended in the label for patients with RLS is 600 mg however; the 600 mg dose was not included in study XP-083. For this reason, the Agency imposed a post-marketing requirement (PMR), the effects of Horizant 600 mg/day on simulated driving. The sponsor submitted a draft protocol April 15, 2011. After review of the protocol, a teleconference was held with the sponsor May 24, 2011 (please refer to Medical Officer (MO) review dated 06/29/2011, for details). The sponsor submitted a revised protocol on an SPA agreement, on June 8, 2011 (MO review dated July 15, 2011). The study (RXP114111) was completed by the sponsor on (October 19, 2011) and the clinical study report (CSR) was submitted as a sNDA on 02/29/2012. The CSR for RXP114111 is subject of this review.

### 2. Background

The sponsor included the results of the two driving studies, XP088 and XP083 in their original NDA for Restless Legs Syndrome (RLS). Study XP088 was *A Pilot Study to Evaluate Driving Simulator Performance and Cognitive Function in Normal Subjects and Subjects with Restless Leg Syndrome*, compared simulated driving in healthy volunteers versus subjects with RLS. Study XP083, *A Randomized, Double-blind, Active and Placebo Controlled, Parallel Group Safety Study Assessing Simulated Driving Performance in XP13512 Treated Patients with Restless Leg Syndrome*, examined the

effect of Horizant (1200mg and 1800mg) compared to placebo and active control, diphenhydramine (DPH) on simulated driving performance, in subjects with RLS.

**Simulated Driving Studies (REVIEWER TABLE)**

Study	Population	Sample Size	Design	Treatment	Driving assessments
XP088	Healthy volunteers vs. RLS	30 (15 Healthy volunteers, 15 RLS)	Parallel group	NA	Day 1 (afternoon), Day 2 (morning)
XP083	RLS	130 (32 GEn 1200mg, 34 GEn 1800mg, 34 PBO, 30 DPH)	Parallel Group	GEn 1200mg, 1800mg, PBO, DPH	Day 14 (evening), Day 15 (morning), Day 16 (Tmax)
RXP114111	Healthy Volunteers	36	Three way crossover	GEn 600mg, PBO, DPH	Day 5 (evening), Day 6 (morning), Day 6 (midday)

At the time of approval the Sponsor agreed to several post-marketing requirements (PMRs), including a study of simulated driving performance in subjects taking Horizant 600 mg compared to placebo and diphenhydramine (active control). The Agency emphasized that the Sponsor must study the duration of clinically significant adverse effects, such as somnolence and impaired simulated driving performance, both over the course of the day (evening, following day) and over time (weeks). The agency and the sponsor discussed the trial design in a teleconference (May 24, 2011). The Sponsor proposed a short-term study in healthy subjects to facilitate the quick turn around of the results. The final protocol included multiple simulated driving assessments in subjects treated for a shorter duration, only 5 days in healthy subject to attempt to expedite completion of the study. The Agency discussed the importance of obtaining information of the duration of an affect on driving in subjects taking the 600 mg dose of Horizant. The Agency noted that the study design would not provide adequate information regarding the duration of detrimental effects on driving or alertness.

This review will examine study RXP114111 in detail and briefly review the results from studies XP088 and XP088 as it relates to the results and interpretation of study RXP-114111. Since the approval of the NDA for RLS, a supplement for using Horizant to treat patients with post herpetic neuralgia (PHN) was approved on (June 6, 2012). The information contained in the label regarding adverse events and information from the clinical reviews of this supplement will be referenced in this review.

This submission does not include data from new efficacy assessments of Horizant in patients with RLS.

### **3. Safety**

#### **Driving Studies:**

#### **Study RXP114111: A Randomized, Double-Blind, Active and Placebo Controlled, Crossover Assessing the Effect of 600mg Gabapentin Enacarbil (GEN) on Simulated Driving in Healthy Subjects**

##### ***Objective***

##### **Primary:**

- To assess the effect of HORIZANT 600mg a day on simulated driving performance in healthy adult subjects

##### **Secondary:**

- To assess the effect of diphenhydramine (DPH) 50mg on simulated driving performance
- To assess the effect of HORIZANT and DPH on a measure of alertness
- To monitor safety and tolerability of repeated dosing of HORIZANT

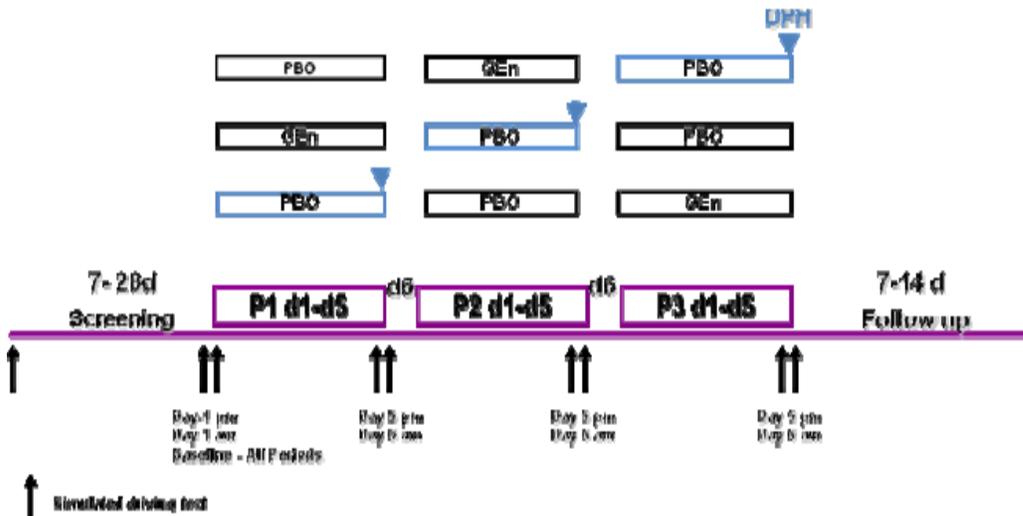
##### ***Design***

The study is a double-blind, double-dummy, placebo- and active-controlled 3-period crossover study. The screening period was within 28 days of the first scheduled dose of study drug. Each subject participated in 3 treatment periods with three driving assessments per treatment period.

All subjects received the following treatments, in random sequence:

Subjects were assigned to one of six sequences in a William's Design (ABC, CBA, BCA, ACB, CAB, BAC) using a 1:1:1:1:1:1 randomization, where A=placebo, B=HORIZANT® 600mg and C=DPH.

### Schematic of RXP-114111 study design



All doses were administered at 5pm in the evening with a standard calorie/fat meal.

Simulated driving tests were conducted:

- **Baseline** prior to start of dosing (**Day -1** in the evening between 7 and 9 pm and **Day 1** in the morning between 7 and 9 am)
- **Day 5** of each treatment period in the evening (between 7 and 9 pm)
- **Day 6** of each treatment period in the morning (between 7 and 9 am)



**Alertness Visual Analog Scale (VAS):**

- The effects of treatment on alertness were assessed by computing the change from baseline compared to the alertness VAS recorded at the pre-driving session minus the VAS at the end of each simulated driving session.
- Adjusted means and 95% CI were calculated for the change from baseline in the difference between pre-driving and post-driving alertness VAS scores using repeated measures mixed model with sequence, period and treatment as fixed effects, subject as random effect and appropriate baseline value as covariate.

**RESULTS:**

**Demographics and Disposition**

The demographics and disposition of subjects is shown in sponsor Table 3.

**Table 3 Summary of Subject Disposition and Demographic Characteristics**

<b>Number of Subjects</b>	<b>Overall N=36</b>
Number of subjects completed, n (%)	35 (97)
Number of subjects discontinued, n (%)	1 (3)
Reasons for discontinuation, n (%)	
Adverse event	1 (3)
Number of subjects in PK Population, n (%)	35 (97)
Number of subjects in ITT Population, n (%)	36 (100)
Number of subjects in Safety Population, n (%)	36 (100)
<b>Demographics</b>	
<b>Age (years), Mean (SD)</b>	36.6 (11.75)
<b>Sex, n (%)</b>	
Female	16 (44)
Male	20 (56)
<b>Height (cm), Mean (SD)</b>	167.36 (7.375)
<b>Weight (kg), Mean (SD)</b>	72.20 (11.438)
<b>Body Mass Index (kg/m<sup>2</sup>), Mean (SD)</b>	25.67 (2.874)
<b>Ethnicity, n (%)</b>	
Hispanic or Latino	21 (58)
Not Hispanic or Latino	15 (42)
<b>Race, n (%)</b>	
African American/African Heritage	9 (25)
Asian - Japanese Heritage	1 (3)
White - White/Caucasian/European Heritage	25 (69)
White and African American/African Heritage	1 (3)

Data Source: Table 9.1, Table 9.3, Table 9.4, and Table 9.5  
 ITT=Intent-to-Treat, PK=pharmacokinetic

**REVIEWER COMMENT:**

The demographic data is notable for a significant difference in mean age among healthy volunteers in study RXP-114111 as compared to patients with RLS. The average age of RLS patients treated in the pivotal efficacy trials (XP052 and XP053) was 51 and 49 years respectively. The mean age of the healthy volunteers in study RXP114111 is 36 years, which is approximately 10-15 years younger than patients with RLS that participated in the pivotal efficacy trials. This raises questions regarding the ability to make inference from the information about the effects Horizant has on driving from study RXP11411 to the population most likely to take Horizant, patients with moderate to severe RLS;

**(REVIEWER TABLE)**

**Mean Age of Subjects in Driving Studies  
 Trials XP052 and XP053 – RLS Patients, Trial RXP114111- Healthy Volunteers**

<b>Trial</b>	<b>N</b>	<b>Mean age (SD)</b>	<b>Min/Max</b>
<b>XP052</b>	220	51 (12.8)	18/81
<b>XP053</b>	321	49 (12.6)	21/77
<b>RXP114111</b>	36	36.6(11.7)	19/57

**Pharmacokinetic Results**

PK samples for GEN were drawn after each simulated driving test. The mean plasma concentration of gabapentin for each driving time point is shown in sponsor Table 6.

**Table 6 Mean (SD) Plasma Concentrations of Gabapentin (ng/mL) by Simulated Driving Time Point (Pharmacokinetic Population)**

<b>N</b>	<b>Simulated Driving Time Point</b>	<b>Mean (SD)</b>	<b>Minimum</b>	<b>Maximum</b>
35	Day 5 evening	1891.9 (823.10)	420	3960
35	Day 6 morning	2084.6 (574.99)	1060	3430
35	Day 6 midday	1164.7 (377.23)	484	2360

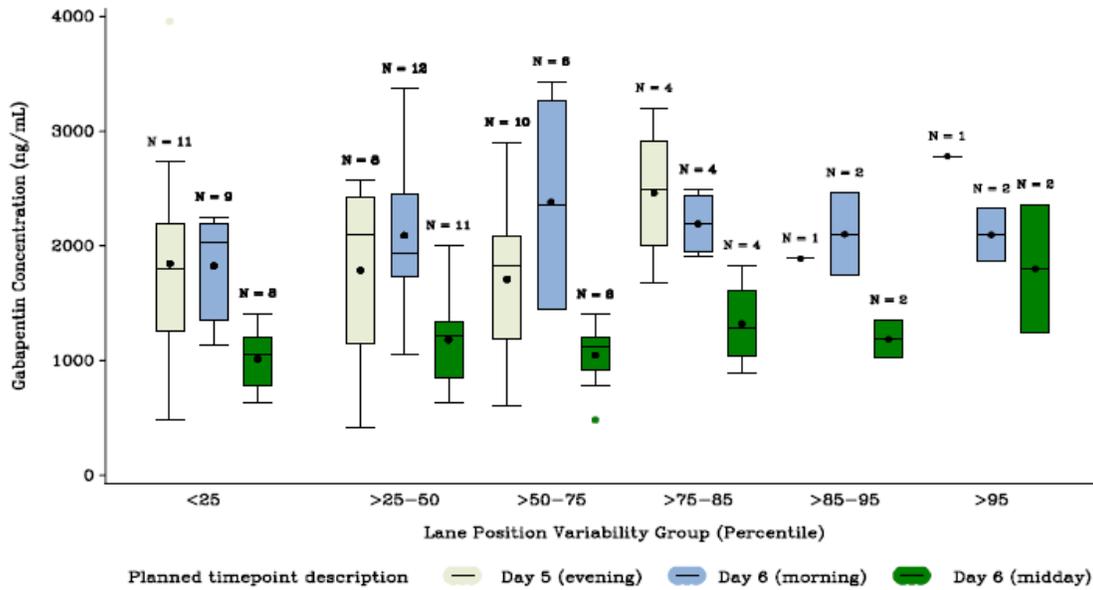
The mean plasma concentration of gabapentin is highest at Day 6 morning time point, approximately 15 hours post dose of Horizant.

**REVIEWER COMMENT:**

The highest mean gabapentin plasma concentrations were reported after the Day 6 morning drive, approximately 15 hours after dosing. Unlike the previous simulated driving study, XP083, there was no PK sample taken at Tmax (6-7 hours post dose).

However, there did not appear to be a relationship between gabapentin plasma concentration and the change in lane position variability (LPV), Sponsor Figure 4.

**Figure 4** Gabapentin Plasma Concentration (ng/mL) Summary by Change in Lane Position Variability Group (Pharmacokinetic Population)



Data Source: [Figure 11.4](#)

Treatment: Gabapentin enacarbil 600 mg

Note: The bottom and top of the box are the 25th and 75th percentiles, the line inside the box is the median, and the symbol is the mean. The ends of the whiskers are the lowest and highest data points still within the 1.5 interquartile range of the lower and upper quartiles, respectively. Data points outside the 1.5 interquartile range are indicated by individual symbols outside the whiskers.

**Primary Endpoint- Change in Lane Position Variability (LPV)**

**Sponsor Table 7 shows the change in LPV for each of the treatment periods, at each simulated driving time point.**

**Table 7 Change in Lane Position Variability (ft) (Intent-to-Treat Population)**

Time Point/ Statistic for LPV (ft)	Baseline N=36	Placebo Treatment Period N=36	GEn 600 mg Treatment Period N=35 <sup>a</sup>	DPH 50 mg Treatment Period N=36 <sup>b</sup>
<b>Day 5 PM</b>				
Mean LPV (SD)	1.24 (0.271)	1.24 (0.276)	1.24 (0.320)	1.40 (0.380)
Change from Baseline:				
Adjusted Mean (SE)		-0.01 (0.041)	-0.01 (0.041)	0.16 (0.041)
Trt Diff vs PBO (95% CI)			-0.01 (-0.09, 0.08)	<b>0.17 (0.08, 0.25)</b>
Trt Diff vs DPH (95% CI)			<b>-0.17 (-0.26, -0.09)</b>	
<b>Day 6 AM</b>				
Mean LPV (SD)	1.30 (0.279)	1.34 (0.303)	1.31 (0.324)	1.33 (0.309)
Change from Baseline:				
Adjusted Mean (SE)		0.04 (0.040)	0.01 (0.040)	0.03 (0.040)
Trt Diff vs PBO (95% CI)			-0.03 (-0.11, 0.04)	-0.01 (-0.08, 0.07)
Trt Diff vs DPH (95% CI)			-0.03 (-0.10, 0.04)	
<b>Day 6 Midday</b>				
Mean LPV (SD)	1.24 (0.259)	1.30 (0.300)	1.28 (0.335)	1.30 (0.318)
Change from Baseline:				
Adjusted Mean (SE)		0.06 (0.031)	0.03 (0.031)	0.06 (0.031)
Trt Diff vs PBO (95% CI)			-0.02 (-0.08, 0.03)	0.00 (-0.05, 0.05)
Trt Diff vs DPH (95% CI)			-0.02 (-0.08, 0.03)	

Data Source: Table 12.1 and Table 12.2

a. N=36 at Baseline.

b. N=35 at Day 5 evening time point.

Note: Bolded cells identify 95% CIs for treatment differences that do not include 0, indicating an apparent difference between the 2 treatments. The analysis method was mixed-model repeated measures with treatment and period as fixed categorical effects, baseline LPV as fixed continuous effect, and subject as a random effect.

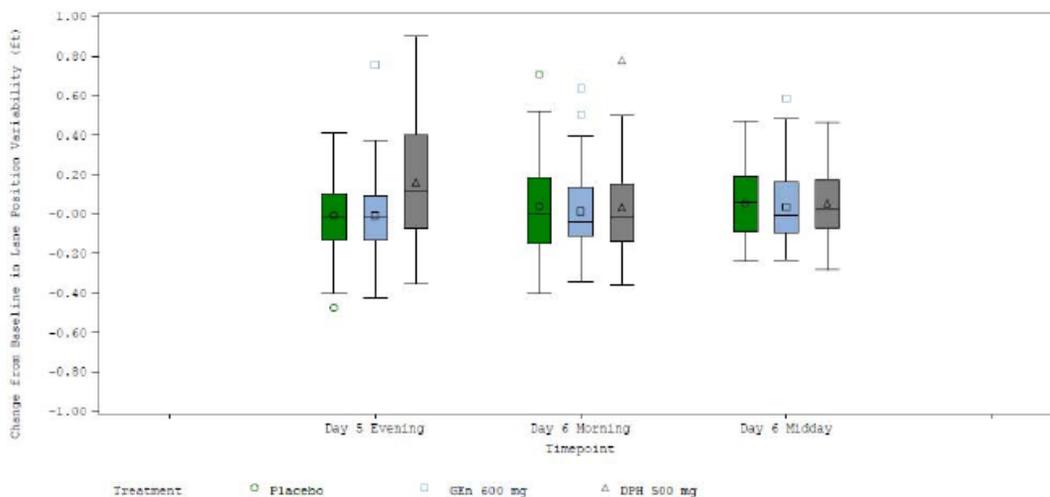
CI=confidence interval, Diff=difference, DPH=diphenhydramine, GEn=gabapentin enacarbil, LPV=lane position variability, PBO=placebo, Trt=treatment, vs=versus

**REVIEWER COMMENT:**

A statistically significant change in LPV from baseline was noted after treatment with diphenhydramine (DPH) during the Day 5 evening simulated driving assessment. There was no statistically significant difference between GEN and placebo at any time point, and no statistically significant difference between DPH and placebo or GEN at morning or midday simulated driving time point.

**Sponsor Figure 5 shows change in LPV from baseline by treatment with outliers.**

**Figure 5 Change from Baseline in Lane Position Variability by Treatment and Time Point (Intent-to-Treat Population)**

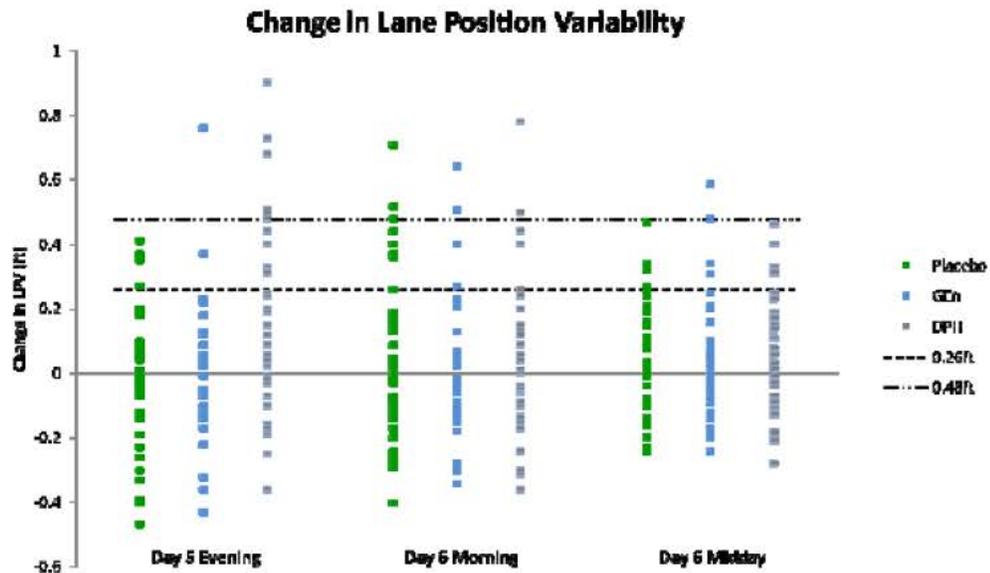


Data Source: [Figure 12.4](#)

Note: The bottom and top of the box are the 25th and 75th percentiles, the line inside the box is the median, and the symbol is the mean. The ends of the whiskers are the lowest and highest data points still within the 1.5 interquartile range of the lower and upper quartiles, respectively. Data points outside the 1.5 interquartile range are indicated by individual symbols outside the whiskers.

DPH=diphenhydramine, GEN=gabapentin enacarbil

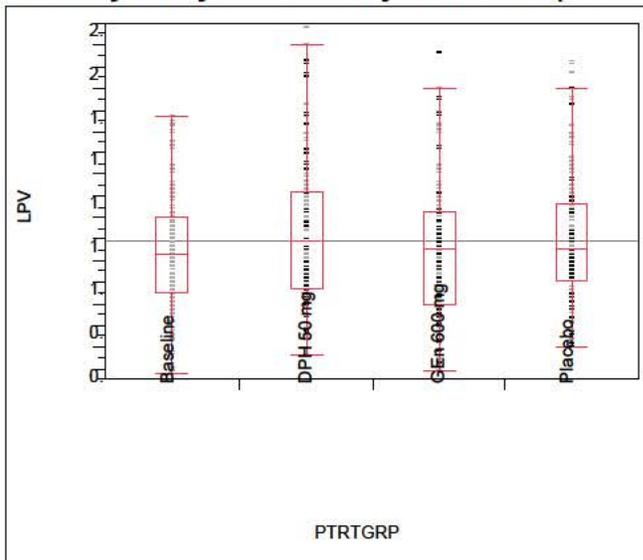
The sponsor defined extreme values of lane position variability as “...those falling in the top 15% of values based on the range of change in LPV across treatment periods and post baseline time points.” (Sponsor figure)



The sponsor's states that the figure shows extreme values (outliers), in all treatment groups.

An independent analysis of outliers, subjects with extreme changes in LPV, was performed by the reviewer. A one-way analysis of change in LPV from baseline by treatment group is presented below.

#### One-way Analysis of LPV by Treatment (PTRTRGP)



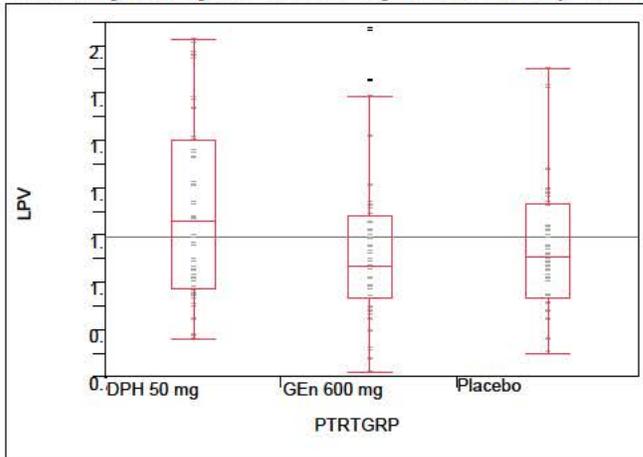
As seen in the box plot, there is not difference significant difference by treatment groups in terms of outliers for LPV.

A further analysis was performed, examining subjects with extreme changes in LPV from baseline, by driving time point.

During Day 5 evening drive, the Gen 600mg group had two outliers for change in lane position variability (LPV).

### DAY 5 – EVENING DRIVE

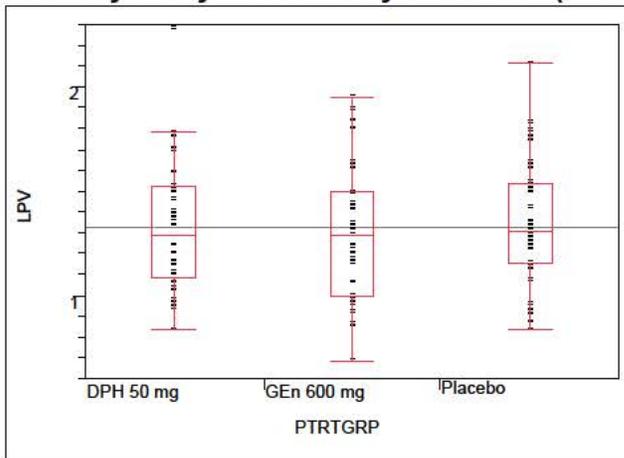
#### One-way Analysis of LPV by Treatment (PTRTGRP)



During Day 6 morning drive, the DPH treatment group had one outlier.

### DAY 6 – MORNING DRIVE

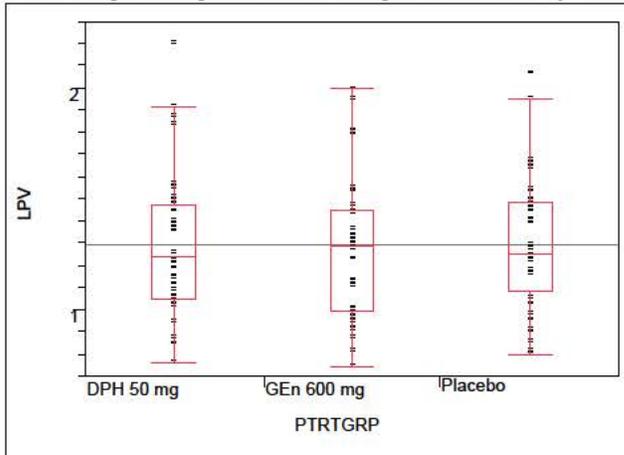
#### One-way Analysis of LPV by Treatment (PTRTGRP)



On Day 6 midday drive; there was one outlier in the DPH treatment group and one outlier in the Placebo group.

### DAY 6 – MIDDAY DRIVE

#### One-way Analysis of LPV by Treatment (PTRTGRP)



#### REVIEWER COMMENT:

As noted from the box plots, outlier analysis of change in LPV from baseline is similar for GEn and placebo at each time point. However, during the Day 5 evening drive, there are more outliers (subjects with greater change in LPV from baseline) during DPH treatment. As noted by the sponsor, an outlier analysis of change in LPV does not show a significant difference between treatments except in the evening for the positive control, DPH, treatment group.

#### Change from baseline in Speed Variability

Sponsor Table 9 shows change from baseline in speed variability by treatment period and time point.

**Table 9 Change in Speed Variability (mph) (Intent-to-Treat Population)**

Time Point/ Statistic for SV (mph)	Baseline N=36	Placebo Treatment Period N=36	GEN 600 mg Treatment Period N=35 <sup>a</sup>	DPH 50 mg Treatment Period N=36 <sup>b</sup>
<b>Day 5 PM</b>				
Mean SV (SD)	1.26 (0.905)	1.29 (0.788)	1.46 (1.501)	1.81 (1.791)
Change from Baseline:				
Adjusted Mean (SE)		0.04 (0.227)	0.21 (0.228)	0.60 (0.228)
Trt Diff vs PBO (95% CI)			0.17 (-0.16, 0.49)	<b>0.56 (0.24, 0.89)</b>
Trt Diff vs DPH (95% CI)			<b>-0.40 (-0.72, -0.07)</b>	
<b>Day 6 AM</b>				
Mean SV (SD)	1.31 (0.739)	1.52 (1.000)	1.53 (1.001)	1.44 (0.769)
Change from Baseline:				
Adjusted Mean (SE)		0.21 (0.125)	0.21 (0.126)	0.12 (0.125)
Trt Diff vs PBO (95% CI)			0.00 (-0.29, 0.29)	-0.09 (-0.37, 0.20)
Trt Diff vs DPH (95% CI)			0.09 (-0.20, 0.37)	
<b>Day 6 Midday</b>				
Mean SV (SD)	1.16 (0.573)	1.44 (0.958)	1.59 (1.161)	1.65 (1.374)
Change from Baseline:				
Adjusted Mean (SE)		0.27 (0.169)	0.42 (0.170)	0.49 (0.169)
Trt Diff vs PBO (95% CI)			0.14 (-0.13, 0.42)	0.22 (-0.06, 0.49)
Trt Diff vs DPH (95% CI)			-0.07 (-0.35, 0.20)	

Data Source: Table 12.4 and Table 12.5

a. N=36 at Baseline.

b. N=35 at Day 5 evening time point.

Note: Bolded cells identify 95% CIs for treatment differences that do not include 0, indicating an apparent difference between the 2 treatments. The analysis method was mixed-model repeated measures with treatment and period as fixed categorical effects, baseline SV as fixed continuous effect, and subject as a random effect.

CI=confidence interval, Diff=difference, DPH=diphenhydramine, GEN=gabapentin enacarbil, PBO=placebo, SV=speed variability, Trt=treatment, vs=versus

**REVIEWER COMMENT:**

During treatment with DPH at evening simulated drive, there is a statistically significant change from baseline in speed variability when compared to placebo. Although not statistically significant, there is a change in speed variability at the Day 6 midday drive for both GEN and DPH treatment periods. As noted below, the majority of crashes occurred for GEN during the day 6 midday driving period.

**CRASHES**

**Sponsor Table 10 shows the number of crashes by treatment period at each time point of simulated driving.**

**Table 10 Number and Percentage of Subjects with Simulated Driving Crashes (Intent-to-Treat Population)**

Time Point/ Number of Simulated Driving Crashes	Baseline N=36 n (%)	Placebo Treatment Period N=36 n (%)	GEn 600 mg Treatment Period N=35 <sup>a</sup> n (%)	DPH 50 mg Treatment Period N=36 <sup>b</sup> n (%)
<b>Day 5 PM</b>				
0	36 (100)	36 (100)	35 (100)	32 (91)
1	0	0	0	2 (6)
2	0	0	0	1 (3)
<b>Day 6 AM</b>				
0	34 (94)	35 (97)	34 (97)	36 (100)
1	2 (6)	1 (3)	1 (3)	0
2	0	0	0	0
<b>Day 6 Midday</b>				
0	35 (97)	36 (100)	32 (91)	33 (92)
1	1 (3)	0	2 (6)	3 (8)
2	0	0	1 (3)	0

Data Source: Table 12.6

a. N=36 at Baseline.

b. N=35 at Day 5 evening time point.

DPH=diphenhydramine, GEn=gabapentin enacarbil

**REVIEWER COMMENT:**

A single subject in the placebo group crashed once during the day 6 morning driving assessment. In the DPH treatment period, there were two subjects with one crash during the Day 5 evening assessment, one subject had two crashes during the Day 5 evening drive and three subjects had one crash during the Day 6 midday drive. In the GEn treatment period there was one subject with one crash in the Day 6 morning simulated drive, two subjects with one crash and one subject with two crashes during the Day 6 midday simulated drive. There were three subjects with crashes at baseline. . One of the subjects who crashed at baseline, also crashed during GEn treatment period (subject ID

(b) (6) There was no apparent correlation between plasma concentration of gabapentin and change in VAS scores (pre versus post driving) and crashes

**INDIVIDUALS WITH CRASHES (Reviewer table)**

SubID	Age	Treatment	Study Day	Timepoint	VAS pre test	VAS post test	Change in LPV	Change in SV	Crashes	Plasma concentration	Extreme LPV value
(b) (6) 33		DPH (GPD)	20	Day 6 Midday	64	33	0.1877	1.1474	2	NA	yes
36		DPH (GDP)	13	Day 6 Midday	90	89	0.2547	1.8445	2	NA	
43		DPH (PGD)	19	Day 5 evening	98	21	0.6832	9.3154	2	NA	yes, at crash
26		DPH (DGP)	5	Day 5 evening	76	42	0.3276	1.1634	2	NA	yes, at crash
19		DPH (PGD)	19	Day 5 evening	29	37	0.9003	2.7896	2	NA	Yes at crash, and midday GEN
		DPH (PDG)	20	Day 6 Midday	65	64	0.3318	1.5199	2	NA	yes at crash
19		GEN (PDG)	20	Day 6 Midday	91	89	-0.046	3.0079	2	1450	Yes at GEN evening
30		GEN (GPD)	6	Day 6 morning	71	36	-0.037	1.5166	1	1830	Yes, all DPH drives
28		GEN (DGP)	13	Day 6 Midday	66	33	0.3068	1.8269	2	1020	yes, all DPH, PBO, GEN morning
21		GEN (DPG)	20	Day 6 Midday	14	35	0.1958	1.7966	1	1830	
28		PBO (GPD)	13	Day 6 morning	38	1	0.7096	2.0893	2	NA	Yes at crash
48		Baseline (PDG)	1	Day 1 midday	98	98	NA	NA	2	NA	
21		Baseline (PGD)	1	Day 1 morning	62	24	NA	NA	2	NA	
19		Baseline (PDG)	1	Day 1 morning	32	36	NA	NA	1	NA	

. Although the mean LPV (calculated over a 10 minute epoch) did not show a correlation with crashes, the raw data for a one minute interval around the crash time, did show an increase in LPV (data not shown).

Individuals, who experienced crashes, during GEn treatment period, are presented in the Reviewer’s Table below. Crashes, mean LPV and SV are presented by epoch. Each epoch is 10 minutes in duration and each simulated drive evaluation consists of 6 epochs for a total60 minutes driving assessment.

**INDIVIDUALS WITH CRASHES DURING GEn TREATMENT PERIOD**

Sub ID	Age	Treatment	Timepoint	Epoch	LPV	SV	Crashes
(b) (6)	19	GEn	Day 6 Midday	<b>1</b>	<b>1.91</b>	<b>6.55</b>	<b>1</b>
				2	1.81	3.84	0
				3	1.46	3.49	0
				4	1.67	3.34	0
				<b>5</b>	<b>1.90</b>	<b>7.32</b>	<b>1</b>
				6	1.89	4.27	0
(b) (6)	30	GEn	Day 6 Morning	1	1.61	0.75	0
				2	1.96	1.00	0
				3	1.82	1.05	0
				<b>4</b>	<b>1.85</b>	<b>5.59</b>	<b>1</b>
				5	1.69	1.20	0
				6	1.67	0.88	0
(b) (6)	28	GEn	Day 6 Midday	1	1.04	0.85	0
				<b>2</b>	<b>1.31</b>	<b>6.00</b>	<b>1</b>
				3	1.22	1.07	0
				4	1.27	0.97	0
				5	1.26	1.07	0
				6	1.41	1.03	0
(b) (6)	21	GEn	Day 6 Midday	1	1.37	0.43	0
				2	1.59	0.51	0
				3	1.36	0.63	0
				<b>4</b>	<b>1.32</b>	<b>4.99</b>	<b>1</b>
				5	1.40	2.30	0
				6	1.35	0.49	0

SV increases during the same epoch in which the subject experiences a crash. A similar association between SV and crashes is noted in subjects who crashed during DPH treatment period. The change in speed variability during crashes may due to an artifact of the simulated driving software. Once a crash occurs, the speed goes to 0 and the lane position is reset to baseline (center of the lane) as well. Of note, one subject (b) (6) who crashed during DPH treatment period had increased speed variability throughout the drive that is even during epochs where there were no crashes.

**Visual Analog Scale (VAS)**

Study subjects were asked to fill out a visual analog scale pre- and post-simulated driving evaluation (Sponsor Appendix C).

**APPENDIX C: Alertness Visual Analog Scale (VAS)**

How alert do you feel now?



\*Score (mm)

--	--	--

\*The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the subject marks.

Results of change in VAS score pre versus posttest are presented in Sponsor Table 11.

**Table 11 Change in Alertness Visual Analogue Scale (mm) (Intent-to-Treat Population)**

Time Point/ Statistic for VAS (mm)	Baseline N=36	Placebo Treatment Period N=36	GEN 600 mg Treatment Period N=35 <sup>a</sup>	DPH 50 mg Treatment Period N=36 <sup>b</sup>
<b>Day 5 PM</b>				
Mean VAS (SD) Change (Pre-Test – Post-Test)	8.7 (17.16)	6.3 (16.18)	4.9 (18.77)	19.0 (23.08)
Change from Baseline:				
Adjusted Mean (SE)		-2.3 (3.22)	-3.7 (3.26)	10.6 (3.26)
Trt Diff vs PBO (95% CI)			-1.4 (-9.80, 7.02)	<b>12.9 (4.50, 21.32)</b>
Trt Diff vs DPH (95% CI)			<b>-14.3 (-22.78, -5.82)</b>	
<b>Day 6 AM</b>				
Mean VAS (SD) Change (Pre-Test – Post-Test)	9.8 (15.98)	11.4 (17.43)	8.8 (25.00)	10.1 (21.26)
Change from Baseline:				
Adjusted Mean (SE)		1.6 (3.57)	-1.3 (3.60)	0.3 (3.57)
Trt Diff vs PBO (95% CI)			-2.9 (-9.93, 4.16)	-1.3 (-8.25, 5.70)
Trt Diff vs DPH (95% CI)			-1.6 (-8.65, 5.44)	
<b>Day 6 Midday</b>				
Mean VAS (SD) Change (Pre-Test – Post-Test)	-0.1 (18.37)	-1.2 (20.84)	3.5 (20.67)	0.3 (17.72)
Change from Baseline:				
Adjusted Mean (SE)		-1.1 (3.27)	3.5 (3.32)	0.4 (3.27)
Trt Diff vs PBO (95% CI)			4.7 (-4.15, 13.45)	1.5 (-7.23, 10.23)
Trt Diff vs DPH (95% CI)			3.2 (-5.65, 11.95)	

Data Source: Table 12.8 and Table 12.9

a. N=36 at Baseline.

b. N=35 at Day 5 evening time point.

Note: Bolded cells identify 95% CIs for treatment differences that do not include 0, indicating an apparent difference between the 2 treatments. The analysis method was mixed-model repeated measures with treatment and period as fixed categorical effects, baseline alertness VAS as fixed continuous effect, and subject as a random effect.

CI=confidence interval, Diff=difference, DPH=diphenhydramine, GEN=gabapentin enacarbil, PBO=placebo, Trt=treatment, VAS=visual analogue scale, vs=versus

**REVIEWER COMMENT:**

Treatment with DPH resulted in a statistically significant difference pre versus post VAS score simulated driving time point, there was, compared to other treatment periods. Of note, the largest mean change pre versus post VAS score for GEN treatment period occurred after the morning simulated driving time point.

To see if there was a correlation between VAS score and crashes, the sponsor was asked (June 29, 2012) to provide an analysis of mean change in somnolence (change in VAS

score), mean LPV, mean speed variability and the number of crashes by driving assessment time point and treatment group, without regard to sequence. The sponsor submitted the analysis on July 6, 2012 (Sponsor Table 1).

**Table 1 Level of Alertness (Indicated by VAS) and Driving Test Results by Time Point Assessed and Treatment Group (Intent-to-Treat Population<sup>1</sup>)**

Time point Assessed	Treatment Group	n	Change in VAS <sup>2</sup> Mean (SD)	LPV (ft) Mean (SD)	SV (mph) Mean (SD)	Crashes		Plasma concentration gabapentin (ng/mL) Mean (SD)
						Subjects <sup>3</sup>	Total <sup>4</sup>	
<b>Day 5 PM</b>								
	Placebo	36	6.3 (16.18)	1.237 (0.2760)	1.285 (0.7878)	0	0	n/a
	Gen	35	4.9 (18.77)	1.237 (0.3197)	1.457 (1.5008)	0	0	1891.9 (823.10)
	DPH	35	19.0 (23.08)	1.398 (0.3797)	1.811 (1.7911)	3	4	n/a
<b>Day 6 AM</b>								
	Placebo	36	11.4 (17.43)	1.339 (0.3026)	1.522 (0.9972)	1	1	n/a
	Gen	35	8.8 (25.00)	1.310 (0.3243)	1.528 (1.0009)	1	1	2084.6 (574.99)
	DPH	36	10.1 (21.26)	1.334 (0.3086)	1.437 (0.7685)	0	0	n/a
<b>Day 6 Midday</b>								
	Placebo	36	-1.2 (20.84)	1.295 (0.3003)	1.435 (0.9582)	0	0	n/a
	Gen	35	3.5 (20.67)	1.280 (0.3348)	1.590 (1.1608)	3	4	1164.7 (377.23)
	DPH	36	0.3 (17.72)	1.297 (0.3179)	1.650 (1.3736)	3	3	n/a

Data Source: Study RXP114111 CSR Tables 12.1, 12.4, 12.6, 12.8, and 11.1.

<sup>1</sup>Intent-to-Treat Population includes all subjects in the Safety Population who completed at least 1 baseline and 1 post-baseline simulated driving assessment.

<sup>2</sup>Change in VAS = (Pre-Test VAS score – Post-Test VAS score) for the driving simulation test conducted at each specified time point. Both the pre-test VAS and post-test VAS scores are taken from the specified time point, and *not* from a separate baseline visit.

<sup>3</sup>Crashes: Subjects is the number of subjects with any 1 or more crashes during the driving simulation test conducted at each specified time point.

<sup>4</sup>Crashes: Total is the total number of crashes occurring across all subjects in the specified treatment group for the specified timepoint. If a subject had more than 1 crash, each crash was counted in this total.

---

**REVIEWER COMMENT:**

As noted in the Sponsor Table, there does not appear to be a correlation between gabapentin plasma levels, change in LPV, or change in VAS (pre versus post drive) and crashes. However, it is notable that all of the crashes during GEN treatment period were on Day 6, the majority during the midday drive.

In study RXP114111 simulated driving assessments were not performed at Tmax for GEN treatment period; therefore one would have to assume that the peak plasma concentration of GEN occurred after the Day 5 drive and before the Day 6 morning and midday drives. However, it is also notable that crashes during DPH treatment period occurred in the Day 6 midday drive in an equal number of subjects as in the Day 5 evening drive (Tmax). Therefore, driving impairment, i.e. crashes, may not be directly related to drug exposure, but rather cause a persistent effect on the CNS and driving behavior.

**ADVERSE EVENTS**

**DEATHS**

No deaths occurred during the study

**SAEs**

There were no SAEs reported during the study.

**Treatment Emergent AEs**

A summary of TEAEs reported by at least two subjects is presented in sponsor table 4.

**Table 4 Summary of Adverse Events Reported in  $\geq 2$  Subjects (Safety Population)**

Preferred Term	Placebo Treatment Period N=36 n (%)	GEN 600 mg Treatment Period N=36 n (%)	DPH 50 mg Treatment Period N=36 n (%)	Overall N=36 n (%)
Number of unique subjects with at least 1 adverse event	9 (25)	10 (28)	11 (31)	18 (50)
Headache	2 (6)	4 (11)	5 (14)	8 (22)
Fatigue	1 (3)	1 (3)	1 (3)	3 (8)
Insomnia	1 (3)	1 (3)	2 (6)	3 (8)
Dizziness	0	1 (3)	1 (3)	2 (6)
Abdominal pain	1 (3)	1 (3)	0	2 (6)
Flatulence	1 (3)	1 (3)	0	2 (6)
Nausea	1 (3)	1 (3)	0	2 (6)
Abnormal dreams	0	1 (3)	1 (3)	2 (6)
Pruritus	2 (6)	0	1 (3)	2 (6)
Skin irritation	2 (6)	0	0	2 (6)
Pollakiuria	0	0	2 (6)	2 (6)

Data Source: Table 10.2

Note: Adverse events in the DPH 50 mg Treatment Period column represents events reported at any time during the treatment period and not just after the single DPH dose received on Day 5.

DPH=diphenhydramine, GEN=gabapentin enacarbil

The most common AE reported by subjects was headache, followed by fatigue and insomnia. The most frequently reported AE in the GEN treatment group was headache (11% GEN, 14% DPH, and 6% PBO). Of note, somnolence, which was the most commonly reported TEAE in subjects with RLS, occurred in one subject (3%) during GEN treatment period.

### **AEs Leading to Withdrawal**

One subject had an AE that led to study drug discontinuation. The subject experienced an abscess in the axilla, before dosing on Day 5 during DPH treatment period. The subject was withdrawn before dosing on Day 4 during the GEN treatment period. The abscess resolved 17 days after onset of symptoms.

**CLINICAL LABORATORY**

One subject experienced elevated AST and ALT during Day 28 follow-up (9 days after last dose of placebo Period 3). The subject was treated with GEN during treatment Period 1 and DPH during treatment Period 2.

<b>LFT parameter</b>	<b>Study Day</b>	<b>Value (Ref Range)</b>
AST	Day 28	198 IU/L (15-44 IU/L)
	Day 30	151 IU/L
	Day 42	30 IU/L
ALT	Day 28	78 IU/L (9-60 IU/L)
	Day 30	89 IU/L
	Day 42	30 IU/L
Creatine Kinase	Day 28	165.3 ukat/L (0.82-6.63 ukat/L)
	Day 30	87.76 ukat/L
	Day 42	3.37 ukat/L

Total and direct bilirubin, GGT, alkaline phosphatase was all normal.

**ECG**

Five subjects were noted to have a change in ECG readings during the study as compared to baseline. One subject had PR interval >220 msec, one subject had QRS < 75msec, one subject had QRS >110 msec, one subject had QTcB >450 msec, but <480 msec and one subject had QTcB change from baseline >30 msec, but <60 msec.

**AEs of Special Concern – Impaired Driving**

The sponsor performed a retrospective review of the GEN clinical trial database for adverse events with preferred term (PT) “road traffic accident” and “impaired driving”. The review is summarized in this section.

The sponsor reviewed, retrospectively, all Phase II and Phase III GEN studies. Of note, these studies were part of the Final Safety Update and Complete Response resubmission (NDA 22399, October 6, 21010) were discussed in detail in Clinical Review dated April 6, 2011.

In brief, the studies totaled 2374 subjects who received at least one dose of GEN. These included 1201 subjects from Phase II and Phase III RLS studies, and 1173 subjects from studies for other indications (PHN, DPN, migraine prophylaxis and RLS-associated sleep disturbance.) Sponsor Table 1.

**Table 1 Enumeration of Unique Subjects Exposed to Investigational Product in Phase II and Phase III GEn Studies**

	Number of Subjects		
	Placebo	GEn	PGB
<b>Individual Phase II and Phase III RLS CDP</b>			
XP052	108	113	-
XP053	96	226	-
XP081	41	176	-
XP083	64 <sup>a</sup>	65	-
XP060	98	326 <sup>c</sup>	-
XP045	33	62	-
XP021	36	36	-
XP055 (GEn Naive subjects only) <sup>b</sup>	-	197	-
<b>Total Phase II and Phase III RLS CDP</b>	<b>476</b>	<b>1201</b>	<b>-</b>
<b>GEn Studies in Other Indications</b>			
PXN110748 (PHN)	95	276	-
XP009 (PHN)	54	47	-
PXN110527 (PHN)	0	94	-
PXN110448 (DPN)	120	234	66
MPX111381 (Migraine Headache Prophylaxis)	128	395	-
RXP110908 (Polysomnography [PSG])	132	127	-
<b>Total Exposures in Other Indications</b>	<b>529</b>	<b>1173</b>	<b>66</b>
<b>Total Exposures in All Phase II and Phase III Studies</b>	<b>1005</b>	<b>2374</b>	<b>66</b>

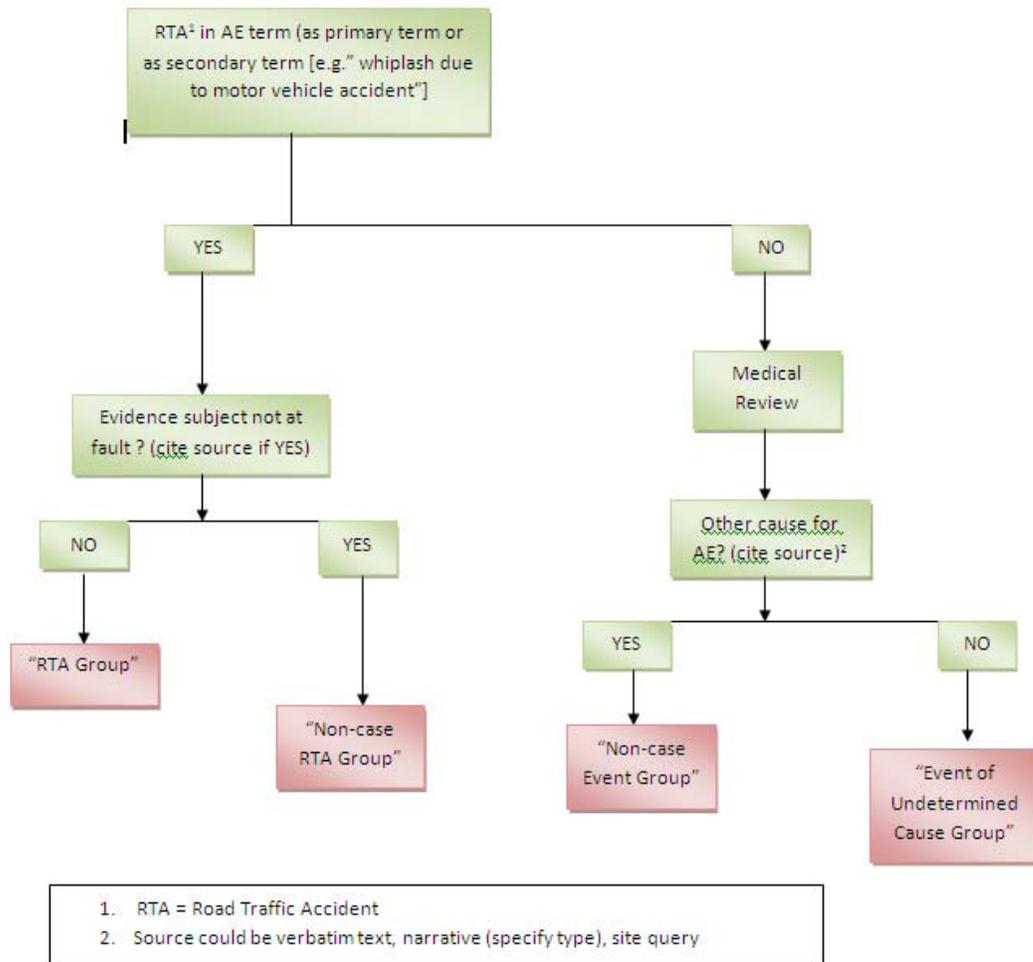
Data Source: Final Safety Update (NDA 022399, 06 October 2010, Sequence 0045), Table 1.2, Table 2.4, Table 3.1, Table 4.1, Table 5.1, Table 6.2, Table 7.1

PGB=pregabalin

- a. Subjects may have received placebo only or placebo and another investigational product.
- b. The 197 GEn Naive subjects in XP055 contribute to both the All RLS Studies total numbers of placebo and GEn subjects, as they participated in a parent study where they received placebo or placebo plus diphenhydramine, and in the open-label extension Study XP055 where they received GEn.
- c. In Study XP060, 326 subjects received GEn during the Single-Blind Phase and 96 of these subjects went on to receive GEn during the double-blind portion of the study.

The sponsor searched the GEn clinical trial database for adverse event of Road Traffic Accident (RTA). An event was classified as an RTA using the algorithm presented in sponsor Figure 1.

**Figure 1 Adjudication Algorithm for Classifying Adverse Events**



The groupings were defined as follows:

- **RTA Group** – All subjects with an RTA as an AE term and for which no definitive information was available to determine that the subject was either not driving or not at fault.
- **Non-Case RTA Group** – All subjects with an RTA as an AE and specific information available which explained that the subject was not driving at the time of the RTA or was hit from behind (e.g. hit from behind while stopped)
- **Non-Case Event Group** – All AEs identified in the clinical database search that did not include RTA in the AE term, but for which there was sufficient evidence that the AE was due to something other than an RTA.

- **Events of Undetermined Cause Group** – If an AE identified in the clinical database search did not meet the criteria for being classified in the RTA Group, Non-Case RTA Group or the Non-Case Event Group, then it was classified in the Events of Undetermined Cause Group. These cases were evaluated for any pattern of trauma that would suggest a possible RTA.

A summary of the retrospective clinical trial database for all defined groups is presented in Sponsor Table 2.

**Table 2 Summary of Retrospective Clinical Trial Database Search for Adverse Events Potentially Related to Impaired Driving (All Phase II/III GEn Studies)**

		Number of Subjects with Event by Group			
		RTA Group <sup>a</sup>	Non-Case RTA Group <sup>b</sup>	Non-Case Events Group <sup>c</sup>	Events of Undetermined Cause Group <sup>d</sup>
<b>All Phase II/III Placebo-Controlled Studies<sup>e</sup></b>					
Placebo	(N=1005)	0	2	9	28
GEn	(N=1853)	2	1	25	73
PGB	(N=66)	1	0	2	1
Neurontin	(N=115) <sup>f</sup>	0	0	0	2
Total <sup>g</sup>		3	3	36	104
<b>Studies/Study Phases without a Placebo Control<sup>h</sup></b>					
GEn	(N=617)	6	5	NA	NA

Data Source: RTA Group: Table 1.1, Table 1.4, Table 1.7, Table 1.10; Table 1.13, Table 1.16;  
 Non-Case RTA Group: Listing 1.2, Listing 1.6, Listing 1.10, Listing 1.14, Listing 1.18, Listing 1.22;  
 Non-Case Event Group: Listing 1.3, Listing 1.11, Listing 1.15, Listing 1.19, Listing 1.23;  
 Events of Undetermined Cause Group: Listing 1.4, Listing 1.12, Listing 1.16, Listing 1.20, and Listing 1.24  
 NA=Not applicable

- Subjects in the RTA Group are discussed further in Section 4.1.
- Subjects in the Non-Case RTA Group are discussed further in Section 4.2.
- Subjects in the Non-Case Event Group are discussed further in Section 4.3.
- Subjects in the Events of Undetermined Cause Group are discussed further in Section 4.4.
- Phase II/III RLS placebo-controlled studies (XP021, XP045, XP052, XP053, XP060 [Double-Blind Phase], XP081, XP083); Phase II/III placebo-controlled studies in other indications (PXN110748, XP009, PXN110448, MPX111381 and RXP110908).
- In Study XP009, 115 subjects received Neurontin during an 11-day open-label Neurontin run-in period prior to randomization.
- No overall total N is presented due to the differing study designs including different study duration.
- RLS Studies XP055 and XP060 [Single-Blind Phase], PHN Study PXN110527.

In the PBO, controlled Phase II/III studies (XP021, XP045, XP052, XP053, XP060, XP081, XP083, PXN110748, XP009, PXN10448, MPX111381, RXP110908), 2 subjects on GEn for migraine (study MPX111381) reported an RTA and one subject on pregabalin (study PXN110448) reported an RTA. In the non-controlled studies, 6 subjects on GEn reported an RTA, and all were subjects with RLS, Sponsor Table 4.

**Table 4 RTA Group: Site Query Information**

Study	Site/Subject #	Treatment/ Phase	Site Query Information
XP060	186- (b) (6)	GEn 1200 mg Single-Blind Phase	lost control over an icy bridge; did not feel tired, groggy or sleepy
XP060	211-	GEn 1200 mg Single-Blind Phase	subject was driving; AEs of Dizziness and sleepiness had resolved prior to that
XP060	213-	GEn 1200 mg Single-Blind Phase	subject was driving at the time of the minor motor vehicle accident; did not feel groggy or have any other adverse events immediately prior to the accident
XP055	128-	GEn Naive (1800 mg)	someone merged into the left lane from the right without seeing the car and struck the side of the vehicle
XP055	148-	GEn Naive (1200 mg)	subject was driving; hit by another car
XP055	205-	GEn Non-Naive (1200 mg)	driving down the road in a very hard rain, the windshield wipers were not operational

Data Source: Appendix 6.5 and Listing 1.21

There were no RTA events in placebo controlled studies for PHN. There was one subject with RTA event on pregabalin, in DPN placebo controlled study, and one subject on GEn 1800mg in the migraine prophylaxis study with RTA event.

**REVIEWER COMMENT:** In the sponsor’s retrospective review of GEn clinical trial database, there were 9 subjects who met criteria for RTA group. Of these subjects, 8 were taking GEn and 1 subject was taking pregabalin. Of the 8 subjects on GEn, 6 were subjects with RLS (all in the long term studies XP055 and XP060) and 2 were subjects with migraine. As noted by the sponsor, the number of subjects considered part of the RTA group is small and therefore difficult to interpret. In addition, it is difficult to analyze data for associations when collected retrospectively.

**POSTMARKETING SAFETY**

The sponsor submitted additional safety data on post-marketing experience of driving impairment with gabapentin and gabapentin enacarbil (m 5.3.6).

**Exposure:** According to the sponsor, since approval of GEn on April 6, 2011 (commercially available June 6, 2011) there have been 12,100 prescriptions filled. The sponsor estimates that this equates to approximately 8,500 patients. In comparison, there are more than 18 years of post-marketing experience with gabapentin (approved in December 1993 as adjunctive therapy for partial seizures and May 2004 for post herpetic neuralgia). The sponsor estimates 30.4 million prescriptions filled for gabapentin, in the US, between January 2011 and November 2011.

**Methods:**

The sponsor performed a search of:

- Their own global safety database, Operating Companies Event Accession and Notification System (OCEANS). This is a global database that

captures all reported suspected adverse drug reactions, including spontaneous AE reports, as well as reports from post-marketing surveillance studies and serious AE reports from clinical trials.

- FDA Adverse Event Reporting System (AERS)
- Literature review using Embase

**Results:**

**OCEANS-** The sponsor used Standardized MedDRA Queries, *Accidents and Injuries*, and then a further search using the Preferred Term (PT) *Impaired Driving Ability*.

The search yielded two spontaneous reports with *Accidents and Injuries* SMQ. Neither case involved driving related accident or injury. The search for PT *Impaired Driving Ability* did not retrieve any cases.

**AERS-** The sponsor used Multi-Item Gamma Poisson Shrinker (MGPS) data mining method to see if there was a relationship between GEN and driving in the AERS database. An empirical Bayes data geometric mean (EBGM) is calculated with 2-sided 90% confidence intervals (EB05, EB95). An  $EB05 \geq 2$  is used as threshold for detection of a signal. This was run against the Q1 2011 public release version of the AERS database. After physician review of 330 PT's, 213 were considered relevant with additional PT *Impaired Driving Ability*, added for 214 physician agreed relevant terms. The results are presented in Sponsor Table 1.

**Table 1 Physician-Agreed Relevant Preferred Terms with Corresponding AERS EB05 Values  $\geq 2$**

Preferred Term	AERS N	AERS EB05
Nerve injury	76	6.039
Road traffic accident	129	2.477
Head injury	96	3.028
Chest injury	9	2.528
Accident	61	2.495
Impaired driving ability	69	3.563
Back injury	28	2.303
Concussion	17	2.109
Haemothorax	14	2.079

Two of the nine terms with  $EB05 > 2$  were relevant for evaluation of the effect of gabapentin on driving, Road Traffic Accident (129 cases) and Impaired Driving Ability (69 cases).

**Literature Review-** A total of 175 articles were retrieved from Embase containing either gabapentin or GEN and at least one term considered synonymous with driving impairment or driving related accident or injury (Sponsor Table 2).

**Table 2 Number of Gabapentin or Gabapentin Enacarbil Articles Containing Terms Synonymous with Impaired Driving or Driving-Related Accidents in Embase as of December 8, 2011**

Search	Results
1) 'road traffic injury' OR 'motor vehicle accidents' OR 'motor vehicle traffic collision' OR 'auto accident' OR 'car accident'/exp OR 'car crash' OR 'car smash' OR 'car wreck' OR 'motor vehicle collision' OR 'personal injury collision' OR 'road accident'/exp OR 'road traffic accident' OR 'road traffic collision' OR 'road traffic incident' OR 'fender bender' OR 'auto car accident' <sup>1</sup>	41,521
2) 'accident'/exp OR 'impaired driving ability' OR 'road traffic accident'	126,063
3) 'gabapentin'/exp OR gabapentin	16,946
4) 'gabapentin enacarbil'/exp OR 'gabapentin enacarbil'	111
5) Search 1) OR Search 2)	126,951
6) Search 3) OR Search 4)	16,946
7) Search 5 AND Search 6 AND [humans]/lim AND [english]/lim	175
1. 'car accident' and 'road accident' mapped to 'traffic accident'; terms exploded	

According to the sponsor, only one article was felt to be relevant (Peterson et al, 2009). This article described the prevalence of gabapentin in impaired driving cases in Washington State between January 2003 and December 2007. Of 23,479 cases of driving impairment submitted for toxicology, 137 cases were positive for gabapentin. However only 9 of 137 cases were positive for gabapentin alone.

The sponsor has concluded, from the post marketing data, that no association between GEN and driving accidents or impaired driving ability was identified. In terms of post-marketing experience with gabapentin, the sponsor notes that the results are consistent with previously identified possible association between gabapentin and road traffic accidents.

**REVIEWER COMMENT:**

Although there does not appear to be an association between GEN and driving impairment in the post marketing data, there are limitations to this type of analysis. Post-marketing data is dependent upon spontaneous and self-reporting. Many subjects taking the medication will be either unaware of the potential association between GEN and impaired driving or reluctant to report impairment in driving, leading to underreporting. In addition, the period of observation, June 2011 to November 2011, is relatively short in assessing post-marketing safety.

## XP088 – A Pilot Study to Evaluate Driving Simulator Performance and Cognitive Function in Normal Subjects and Subjects with Restless Leg Syndrome

### RESULTS:

#### Demographics and Disposition

A summary of the Demographics of the study population is presented in sponsor Table 3.

**Table 3 Summary of Demographic Characteristics (Normal and RLS Populations: Study XP088)**

	Normal N=15	RLS N=15	Total N=30
<b>Age (years), N</b>	<b>15</b>	<b>14</b>	<b>29</b>
Mean (SD)	35.9 (9.13)	52.6 (12.6)	44.0 (13.7)
Range	19.5-51.9	27.4-73.6	19.5-73.6
<b>Gender, N</b>	<b>15</b>	<b>15</b>	<b>30</b>
Male, n (%)	7 (46.7)	6 (40.0)	13 (43.3)
Female, n (%)	8 (53.3)	9 (60.0)	17 (56.7)
<b>Race, N</b>	<b>14</b>	<b>15</b>	<b>29</b>
White or Caucasian, n (%)	11 (73.3)	15 (100.0)	26 (86.7)
Black or African-American, n (%)	3 (20.0)	0 (0.0)	3 (10.0)
<b>Ethnicity, N</b>	<b>14</b>	<b>15</b>	<b>29</b>
Hispanic/Latino, n (%)	1 (6.7)	0 (0.0)	1 (3.3)
Not Hispanic/Latino, n (%)	13 (86.7)	15 (100.0)	28 (93.3)
<b>Weight (kg), N</b>	<b>14</b>	<b>14</b>	<b>28</b>
Mean (SD)	79.0 (16.3)	79.5 (13.6)	79.2 (14.7)
Range	52.4-104.3	58.8-111.6	52.4-111.6
<b>Height (cm), N</b>	<b>12</b>	<b>11</b>	<b>23</b>
Mean (SD)	170.7 (7.73)	167.1 (9.08)	169.0 (8.41)
Range	163-188	152-180	152-188
<b>Epworth Sleepiness Scale Score<sup>1</sup>, N</b>	<b>15</b>	<b>15</b>	<b>30</b>
Mean (SD)	5.2 (3.23)	8.9 (2.96)	7.1 (3.59)
Range	0-12	3-16	0-16

Data Source: Table 6.2.

1. Higher scores indicate greater severity of symptoms.

#### Primary Endpoint- Change in Lane Position Variability (LPV)

The primary endpoint of change in LPV was similar between the two populations (Sponsor Tables 8).

**Table 8 Lane Position Variability (Normal and RLS Populations: Study XP088)**

	Normal N=15	RLS N=15	Total N=30
<b>Day 1, 4PM – Overall (0 to 60 min)</b>			
Mean (SD)	1.3 (0.58)	1.2 (0.31)	1.2 (0.46)
Median (Range)	1.2 (0.6-3.1)	1.2 (0.7-2.0)	1.2 (0.6-3.1)
95% CI	0.9, 1.6	1.0, 1.4	-
<b>Day 2, 8AM – Overall (0 to 60 min)</b>			
Mean (SD)	1.6 (1.07)	1.2 (0.28)	1.4 (0.79)
Median (Range)	1.2 (0.6-5.2)	1.2 (0.9-1.8)	1.2 (0.6-5.2)
95% CI	1.0, 2.2	1.1, 1.4	-

Data Source: Table 7.4.

Note: Lane position variability was the standard deviation of lane position, where lane position was measured once per second during the indicated time interval. The range of values for lane position was -18 to 18 feet, where the paved roadway was between -13 and 13 feet and 6.5 feet was the center of the lane to the right of the center lane.

### Change from baseline in Speed Variability

The secondary endpoint, change in speed variability was also similar for the two populations (Sponsor Table 10).

**Table 10 Speed Variability (Normal and RLS Populations: Study XP088)**

	Normal N=15	RLS N=15	Total N=30
<b>Day 1, 4PM – Overall (0 to 60 min)</b>			
Mean (SD)	3.0 (1.09)	3.4 (0.90)	3.2 (1.00)
Median (Range)	3.0 (1.5-5.8)	3.5 (2.0-4.8)	3.0 (1.5-5.8)
95% CI	2.3, 3.6	2.9, 3.9	-
<b>Day 2, 8AM – Overall (0 to 60 min)</b>			
Mean (SD)	2.9 (1.02)	3.3 (1.30)	3.1 (1.17)
Median (Range)	2.9 (1.4-5.4)	3.2 (1.4-6.8)	3.2 (1.4-6.8)
95% CI	2.3, 3.5	2.6, 4.1	-

Data Source: Table 7.6.

Note: Speed variability was the standard deviation of the vehicle's speed (mph), where speed was measured once per second over the indicated time interval.

### CRASHES

Although both groups had the same number of subjects with crashes, the RLS subjects experienced more total crashes than did the healthy volunteers (Sponsor Table 11).

**Table 11 Number of Crashes (Normal and RLS Populations: Study XP088)**

	Normal N=15	RLS N=15	Total N=30
<b>Day 1, 4PM – Overall (0 to 60 min), n (%)</b>			
0 Crashes	13 (86.7)	15 (100.0)	28 (93.3)
1 Crash	2 (13.3)	0 (0.0)	2 (6.7)
2 Crashes	0 (0.0)	0 (0.0)	0 (0.0)
3 Crashes	0 (0.0)	0 (0.0)	0 (0.0)
<b>Day 2, 8AM – Overall (0 to 60 min), n (%)</b>			
0 Crashes	15 (100.0)	13 (86.7)	28 (93.3)
1 Crash	0 (0.0)	1 (6.7)	1 (3.3)
2 Crashes	0 (0.0)	0 (0.0)	0 (0.0)
3 Crashes	0 (0.0)	1 (6.7)	1 (3.3)

Data Source: Table 7.7.

Note: Number of crashes over the indicated time interval, where the simulated vehicle went off the 26-foot wide roadway by more than 5 feet or hit an oncoming vehicle.

**REVIEWER COMMENT:** As seen study RXP11411, all the crashes in RLS subjects, in study XP088, occurred the next morning.

In the study report for XP088, the sponsor noted that although the results were similar on the primary endpoint, between subjects with RLS and healthy volunteers, there were differences in crashes experienced (CSR XP088 Section 9.1.2.1).

**9.1.2.1. RLS and Driving Performance**

RLS subjects were similar to normal subjects with regard to lane position variability, speed variability, and brake reaction time during both driving simulator tests. For speed variability by epoch comparing groups, it is noted that there was increased variability for three RLS subjects seen in the later epochs for the Day 2 (AM) drive. RLS subjects also had twice as many crashes than normal subjects (4 crashes vs. 2 crashes), although the number of subjects who experienced crashes was the same for both groups.

Within-group comparisons between the afternoon (Day 1) and morning (Day 2) driving tests showed that RLS subjects had crashes at Epochs 5 and 6 in the morning (Day 2) test; whereas, normal subjects had crashes at Epochs 3 and 5 in the afternoon (Day 1) test. For all other driving measurements (lane position, lane position variability, speed variability, and brake reaction time) both groups had similar results for the afternoon (Day 1) and morning (Day 2) driving tests.

The timing of the crashes coincided with the augmentation of speed variability and, to some extent, lane position variability, in both populations. Two of the 3 RLS subjects whose speed variability deteriorated during the last 2 epochs experienced crashes at

the same time. The worsening of driving performance in the later epochs of the test observed in these RLS individuals is typically seen in subjects with sleep disorders or sleep deprivation [Risser, 2000; Ware, 2006; May, 2005] and suggests that sleep disturbance caused by RLS may affect driving performance in selected subjects whose psychomotor function may be more prone to sleep deprivation.

## VAS

In study XP088, the VAS scores for subjects with RLS were lower (less alert) pre versus post simulated driving in the afternoon and next morning, as compared to healthy volunteers (Sponsor Table 14).

**Table 14 Alertness VAS Assessment (Normal and RLS Populations: Study XP088)**

	Normal N=15	RLS N=15	Total N=30
<b>Day 1, 4 PM – Pre-drive VAS (mm)<sup>1</sup></b>			
Mean (SD)	72.1 (12.93)	56.1 (16.59)	64.1 (16.74)
Median (Range)	71 (49-91)	56 (35-96)	66 (35-96)
95% CI	65.0, 79.3	46.9, 65.3	-
<b>Day 1, 4 PM – Post-drive VAS (mm)<sup>1</sup></b>			
Mean (SD)	47.7 (14.49)	31.7 (18.74)	39.7 (18.38)
Median (Range)	50 (22-73)	27 (2-61)	41 (2-73)
95% CI	39.7, 55.8	21.3, 42.0	-
<b>Day 2, 8 AM – Pre-drive VAS (mm)<sup>1</sup></b>			
Mean (SD)	59.7 (19.32)	51.1 (19.25)	55.4 (19.45)
Median (Range)	59 (27-90)	53 (23-91)	55 (23-91)
95% CI	49.0, 70.4	40.5, 61.8	-
<b>Day 2, 8 AM – Post-drive VAS (mm)<sup>1</sup></b>			
Mean (SD)	45.5 (20.92)	30.5 (25.14)	38.0 (23.96)
Median (Range)	44 (11-81)	29 (1-80)	35 (1-81)
95% CI	33.9, 57.1	16.6, 44.5	-

Data Source: Table 7.1.

1. Visual analog scale (VAS) with anchor points 'Extremely Sleepy' (0mm) and 'Extremely Alert' (100mm).

**REVIEWER COMMENT:** Of note, the VAS scores for the subjects with RLS were lower (less alert) at baseline compared to healthy volunteers. In addition, Epworth Sleepiness Scale Score (ESS) was higher at baseline for RLS subjects compared to healthy volunteers, 8.9 versus 5.2. The ESS was not administered after driving or the next morning. However, the Pittsburgh Sleep Diary was administered to all subjects prior to driving on Day 1 (4PM) and prior to driving on Day 2 (8AM). Subjects with RLS have poor sleep quality as seen by the diary scores for Pittsburgh Sleep Diary (Sponsor Table 5).

**Table 5 Pittsburgh Sleep Diary Results (Normal and RLS Populations: Study XP088)**

	Normal N=15	RLS N=15	Total N=30
<b>Prior to Day 1</b>			
<b>Total Sleep Time (min)</b>	<b>15</b>	<b>15</b>	<b>30</b>
Mean (SD)	471.6 (124.17)	420.1 (95.24)	445.8 (111.84)
Range	215 - 690	135 - 535	135 - 690
<b>Wake Time After Sleep Onset (min)</b>	<b>15</b>	<b>15</b>	<b>30</b>
Mean (SD)	2.2 (4.48)	23.5 (24.90)	12.9 (20.66)
Range	0 - 15	0 - 90	0 - 90
<b>Sleep Quality (mm)<sup>1</sup></b>	<b>15</b>	<b>15</b>	<b>30</b>
Mean (SD)	70.6 (12.00)	47.0 (26.87)	58.8 (23.71)
Range	48 - 94	3 - 98	3 - 98
<b>Prior to Day 2</b>			
<b>Total Sleep Time (min)</b>	<b>13</b>	<b>14</b>	<b>27</b>
Mean (SD)	389.0 (91.95)	353.1 (91.70)	370.4 (91.88)
Range	240 - 535	150 - 460	150 - 535
<b>Wake Time After Sleep Onset (min)</b>	<b>14</b>	<b>15</b>	<b>29</b>
Mean (SD)	5.4 (8.12)	27.7 (23.59)	16.9 (20.92)
Range	0 - 20	0 - 90	0 - 90
<b>Sleep Quality (mm)<sup>1</sup></b>	<b>15</b>	<b>15</b>	<b>30</b>
Mean (SD)	64.5 (17.37)	43.4 (20.10)	53.9 (21.34)
Range	35 - 86	11 - 75	11 - 86

Data Source: Table 6.3.

1. Visual analog scale (VAS) with anchor points "very bad" (0 mm) and "very good" (100 mm).

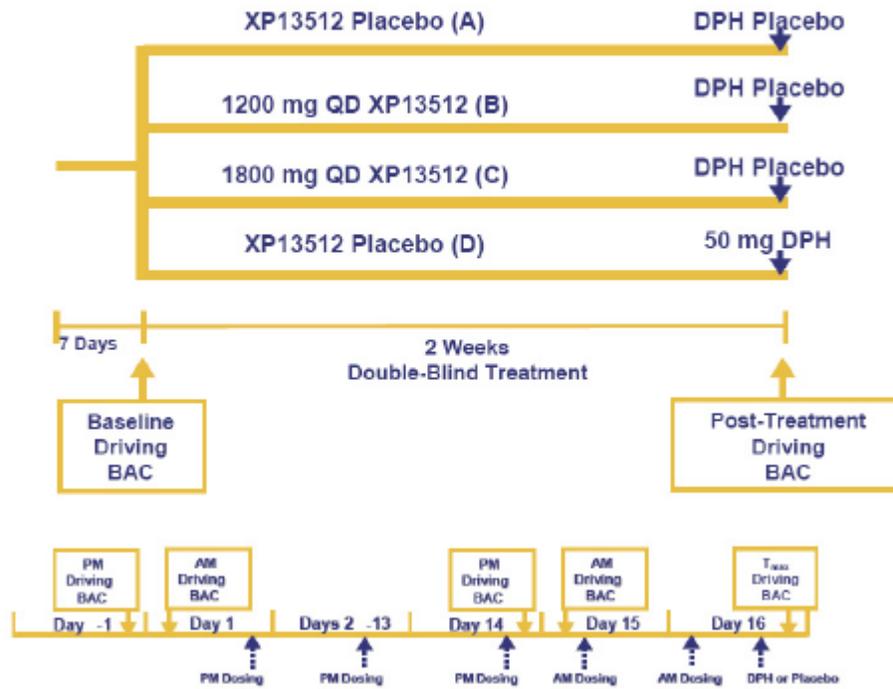
### **Study XP083:- A Randomized, Double-blind, Active and Placebo Controlled, Parallel Group Safety Study Assessing Simulated Driving Performance in XP13512 Treated Patients with Restless Leg Syndrome**

#### **DESIGN**

The primary endpoint in study XP083 was the change from baseline (Day 1) in overall lane position variability (LPV) measured by simulated driving performance at the estimated time to maximum drug concentration (Tmax) on Day 16. Under normal prescribing conditions, the drug would be given at 5pm with Tmax occurring at approximately midnight. In order for the subject to be awake during driving time, the drug was given at 11am on Day 16 and driving was tested at Tmax, approximately 7 hours after dosing. Of note, diphenhydramine was given two hours prior to simulated driving test on Day 16. Day -1(evening) was used as baseline for change in LPV on Day 16.

Two additional time points were also employed as secondary measurements. On Day 14, simulated driving was tested approximately two hours after treatment with GEN and again the following morning (Day 15) approximately 14-16 hours post dose. Neither of these time points used an active comparator (diphenhydramine) only comparison to placebo.

**Figure 1 Overall Study Design**



**DOSE:**

On Day 14, subjects took GEN or placebo (PBO) in the evening. On Day 15, subjects took GEN or PBO in the morning. On Day 16, subjects took GEN or PBO in the morning, and diphenhydramine (DPH) or PBO in the evening (2 hours before simulated driving assessment).

## RESULTS

### Demographics and Disposition

**Table 7 Summary of Demographic Characteristics (Safety Population)**

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH	Total
	N=34	N=31	N=34	N=30	N=129
<b>Age (years)</b>					
Mean (SD)	49.6 (11.40)	46.8 (11.31)	49.3 (10.27)	40.6 (11.80)	46.8 (11.62)
Range	25.0-70.0	22.0-66.0	27.0-65.0	21.0-62.0	21.0-70.0
<b>Gender, n (%)</b>					
Female	20 (58.8)	21 (67.7)	17 (50.0)	19 (63.3)	77 (59.7)
Male	14 (41.2)	10 (32.3)	17 (50.0)	11 (36.7)	52 (40.3)
<b>Race, n (%)</b>					
White or Caucasian	34 (100.0)	31 (100.0)	33 (97.1)	30 (100.0)	128 (99.2)
Other	0	0	1 (2.9)	0	1 (0.8)
<b>Ethnicity, n (%)</b>					
Hispanic/Latino	4 (11.8)	3 (9.7)	4 (11.8)	3 (10.0)	14 (10.9)
Not Hispanic/Latino	30 (88.2)	28 (90.3)	30 (88.2)	27 (90.0)	115 (89.1)

Data Source: DS Table 6.6

PK results for each time point are presented in sponsor Table 45.

### PK Results

**Table 45 Gabapentin Blood Concentrations (ng/mL) at Days 14, 15, and 16 (Safety Population)**

	XP13512 1200 mg			XP13512 1800 mg		
	Day 14	Day 15	Day 16	Day 14	Day 15	Day 16
	N=28	N=28	N=26	N=33	N=33	N=33
Mean (SD)	2580.0 (1428.0)	4257.1 (1621.6)	6355.2 (2348.0)	3448.9 (1858.0)	5824.8 (2056.2)	10082.5 (3735.1)
Median	2335	4160	6425	3240	5200	9160
Min, Max	103, 5800	180, 7770	656, 11500	864, 8900	2460, 11800	4440, 19800

Data Source: DS Listing 26

### Primary Endpoint- Change in Lane Position Variability (LPV)

The results of change in LPV from baseline (Day -1) to Day 16 are shown in sponsor table 11.

**Table 11 Lane Position Variability at Baseline (Day -1) and Day 16, and Change from Baseline (Day -1) to Day 16 in Overall (0 to 60 minutes) Lane Position Variability in Feet (MITT Population)**

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH <sup>a</sup>	95% CI for Mean	95% CI for LS Mean
	N=33	N=28	N=33	N=28		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Baseline (Day -1)	1.40 (0.32)	1.46 (0.32)	1.37 (0.20)	1.36 (0.25)		
Day 16	1.26 (0.31)	1.61 (0.48)	1.52 (0.37)	1.52 (0.50)		
Change from Baseline to Day 16						
Mean (SD)	-0.11 (0.17)	0.15 (0.38)	0.15 (0.27)	0.16 (0.40)		
LS Mean (SE)	-0.10 (0.06)	0.15 (0.06)	0.15 (0.06)	0.16 (0.06)		
XP13512 1200 mg - Pbo					0.10, 0.41	0.08, 0.42
XP13512 1800 mg - Pbo					0.14, 0.37	0.09, 0.41
Pbo/DPH - Pbo					0.10, 0.43	0.09, 0.42
XP13512 1200 mg - Pbo/DPH					-0.22, 0.20	
XP13512 1800 mg - Pbo/DPH					-0.18, 0.17	

Data Source: DSTable 8.4 and DSTable 9.4

- a. Pbo/DPH group received diphenhydramine on Day 16 only.
- b. Analysis was based on a repeated measures ANOVA model with fixed effects for treatment group, pooled site, visit and treatment group by visit

**REVIEWER COMMENT:**

Although the primary endpoint for the study was change in LPV at Tmax (Day 16), patients with RLS will be taking the medication at 5pm and most likely not driving until the next day. Study Day 15 captures this scenario. Subjects take study drug at 5pm, the night before, and then undergo testing the following morning (approximately 14-16 hours after taking study drug). The results of change in LPV from baseline to Day 15 (outlined in red) are shown in sponsor table 12.

**Table 12 Lane Position Variability at Baseline (Day -1 and Day 1), Day 14, and Day 15, and Change from Baseline (Day -1 or Day 1) to Day 14 and Day 15 in Overall (0 to 60 minutes) Lane Position Variability (MITT Population)**

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH <sup>a</sup>	95% CI for Mean	ANOVA <sup>b</sup>
	N=33	N=28	N=33	N=28		95% CI for LS-Mean
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Baseline (Day -1)	1.40 (0.32)	1.46 (0.32)	1.37 (0.20)	1.36 (0.25)		
Day 14	1.34 (0.38)	1.62 (0.62)	1.36 (0.38)	1.29 (0.26)		
Change from Baseline (Day -1) to Day 14						
Mean	-0.06 (0.17)	0.17 (0.43)	-0.01 (0.28)	-0.08 (0.15)		
LS Mean	-0.06 (0.05)	0.17 (0.05)	-0.01 (0.05)	-0.08 (0.05)		
XP13512 1200 mg – Pbo					0.06, 0.39	0.09, 0.37
XP13512 1800 mg – Pbo					-0.06, 0.17	-0.08, 0.19
Baseline (Day 1)	1.35 (0.28)	1.49 (0.36)	1.40 (0.29)	1.45 (0.35)		
Day 15	1.35 (0.31)	1.62 (0.45)	1.44 (0.46)	1.34 (0.26)		
Change from Baseline (Day 1) to Day 15						
Mean	-0.01 (0.14)	0.13 (0.40)	0.02 (0.32)	-0.10 (0.19)		
LS Mean	-0.01 (0.05)	0.13 (0.05)	0.02 (0.05)	-0.10 (0.05)		
XP13512 1200 mg – Pbo					-0.01, 0.29	-0.00, 0.26
XP13512 1800 mg – Pbo					-0.10, 0.15	-0.12, 0.16

Data Source: DSTable 8.4 and DSTable 9.4

- a. Pbo/DPH group received diphenhydramine on Day 16 only.
- b. Analysis was based on a repeated measures ANOVA model with fixed effects for treatment group, pooled site, visit, and treatment group by visit.

Overall, subjects on study drug performed worse on the primary endpoint, change in LPV, in the simulated driving evaluation on Day 15 than placebo; DPH was not administered during this visit. Interestingly, GEN 1200mg cohort had greater change in LPV than GEN 1800mg cohort Please refer to NDA 22399 review dated (02/9/2010?).

### Change from baseline in Speed Variability

**Table 13** Speed Variability (mph) at Baseline (Day -1 and Day 1), Day 14, Day 15, and Day 16, and Change from Baseline (Day -1 or Day 1) to Day 14, Day 15, and Day 16 in Overall (0 to 60 minutes) Speed Variability (MITT Population)

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH <sup>a</sup>	95% CI for Mean	ANOVA <sup>b</sup>
	N=33	N=28	N=33	N=28		95% CI for LS Mean
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		Mean
Baseline (Day -1)	2.75 (0.74)	3.45 (1.70)	2.99 (1.05)	3.14 (1.38)		
Baseline (Day 1)	2.59 (0.84)	3.01 (1.24)	2.64 (0.87)	2.96 (1.09)		
Day 14	2.53 (0.96)	3.26 (2.04)	2.67 (0.94)	2.67 (1.26)		
Change from Baseline (Day -1) to Day 14						
Mean (SD)	-0.22 (0.63)	-0.19 (1.42)	-0.32 (1.17)	-0.47 (0.96)		
LS Mean (SE)	-0.24 (0.19)	-0.18 (0.20)	-0.31 (0.19)	-0.46 (0.20)		
XP13512 1200 mg - Pbo					-0.52, 0.58	-0.49, 0.60
XP13512 1800 mg - Pbo					-0.57, 0.36	-0.60, 0.44
Day 15	2.34 (0.80)	3.44 (2.19)	2.58 (0.82)	2.60 (1.09)		
Change from Baseline (Day 1) to Day 15						
Mean (SD)	-0.26 (0.48)	0.43 (2.22)	-0.07 (0.69)	-0.33 (0.43)		
LS Mean (SE)	-0.29 (0.21)	0.44 (0.22)	-0.06 (0.21)	-0.34 (0.23)		
XP13512 1200 mg - Pbo					-0.11, 1.50	0.13, 1.33
XP13512 1800 mg - Pbo					-0.10, 0.49	-0.36, 0.81
Day 16	2.07 (0.65)	3.33 (2.01)	3.23 (2.08)	3.06 (1.54)		
Change from Baseline (Day -1) to Day 16						
Mean (SD)	-0.54 (0.55)	-0.12 (2.02)	0.23 (1.95)	-0.08 (1.11)		
LS Mean (SE)	-0.57 (0.28)	-0.11 (0.29)	0.24 (0.27)	-0.08 (0.29)		
XP13512 1200 mg - Pbo					-0.35, 1.19	-0.35, 1.26
XP13512 1800 mg - Pbo					0.04, 1.51	0.03, 1.58
Pbo/DPH - Pbo					0.01, 0.92	-0.32, 1.30
XP13512 1200 mg - Pbo/DPH					-0.92, 0.83	
XP13512 1800 mg - Pbo/DPH					-0.52, 1.14	

Data Source: DSTable 8.6 and DSTable 9.4

a. Pbo/DPH group received diphenhydramine on Day 16 only.

b. Analysis was based on a repeated measures ANOVA model with fixed effects for treatment group, pooled site, visit, and treatment group by visit.

### REVIEWER COMMENT:

Mean changes in SV increased the most for GEn 1200mg on Day 15, and GEn 1800mg Day 16. As noted below, the increase in mean change for speed variability is associated with the days the subjects experienced the most crashes (Sponsor Table 14).

### CRASHES

As seen in Sponsor Table 14, there is a correlation between simulated crashes and treatment.

(Source: Sponsor)

**Table 14 Number of Subjects with Simulated Crashes at Baseline and Days 14, 15, and 16 (MITT Population)**

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH <sup>a</sup>
	N=33	N=28	N=33	N=28
<b>Number of Subjects with Crashes, n (%)</b>				
Day -1	3 (9.1)	6 (21.4)	3 (9.1)	2 (7.1)
Day 1	1 (3.1)	4 (14.3)	3 (9.4)	3 (11.1)
Day 14	4 (12.1)	6 (21.4)	1 (3.0)	1 (3.6)
Day 15	1 (3.0)	10 (35.7)	1 (3.2)	0 (0)
Day 16	0 (0)	8 (28.6)	6 (18.2)	3 (10.7)

Data Source: DSTable 8.7.1

a. Pbo/DPH group received diphenhydramine on Day 16 only.

RLS subjects on Gen (1200mg>1800mg) have the greatest number of crashes overall.

The distribution of subjects by number of simulated crashes is presented for each driving assessment time point in sponsor table 15.

**Table 15 Distribution of Subjects by Number of Simulated Crashes at Baseline and Days 14, 15, and 16 (MITT Population)**

	Pbo N=33	XP13512 1200 mg N=28	XP13512 1800 mg N=33	Pbo/DPH <sup>a</sup> N=28
<b>Day -1, Overall (0 to 60 minutes), n (%)</b>				
N	33	28	33	28
1 Crash	2 (6.1)	4 (14.3)	3 (9.1)	2 (7.1)
2 Crashes	0	1 (3.6)	0	0
3 Crashes	1 (3.0)	1 (3.6)	0	0
<b>Day 1, Overall (0 to 60 minutes), n (%)</b>				
N	32	28	32	27
1 Crash	0	2 (7.1)	3 (9.4)	3 (11.1)
2 Crashes	1 (3.1)	0	0	0
3 Crashes	0	2 (7.1)	0	0
<b>Day 14, Overall (0 to 60 minutes), n (%)</b>				
N	33	28	33	28
1 Crash	2 (6.1)	1 (3.6)	0	1 (3.6)
2 Crashes	2 (6.1)	2 (7.1)	0	0
3 Crashes	0	0	1 (3.0)	0
4 Crashes	0	1 (3.6)	0	0
5 Crashes	0	1 (3.6)	0	0
13 Crashes	0	1 (3.6)	0	0
<b>Day 15, Overall (0 to 60 minutes), n (%)</b>				
N	33	28	31	28
1 Crash	1 (3.0)	4 (14.3)	1 (3.2)	0
2 Crashes	0	3 (10.7)	0	0
4 Crashes	0	2 (7.1)	0	0
13 Crashes	0	1 (3.6)	0	0
<b>Day 16, Overall (0 to 60 minutes), n (%)</b>				
N	30	28	33	28
1 Crash	0	5 (17.9)	3 (9.1)	2 (7.1)
3 Crashes	0	1 (3.6)	2 (6.1)	0
4 Crashes	0	1 (3.6)	0	0
5 Crashes	0	0	0	1 (3.6)
13 Crashes	0	0	1 (3.0)	0
17 Crashes	0	1 (3.6)	0	0

Data Source: DSTable 8.7.1

Note: Number of crashes over the indicated time interval, defined as a collision with an oncoming car or obstacle (e.g., tree), or when the vehicle deviated from the center line greater than 18 ft. on either side of the road.

a. Pbo/DPH group received diphenhydramine on Day 16 only.

RLS subjects in GEN treatment group (1200mg>1800mg) have the greatest number of subjects with multiple crashes.

**REVIEWER COMMENT:** Only one subject on placebo had greater than two crashes and this occurred during baseline drive. However, in GEN treatment group, 13 subjects (8 on GEN 1200mg/day and 5 on GEN 1800mg/day) had > 2 crashes. All of the subjects with multiple crashes in the GEN 1800mg treatment group had multiple crashes after treatment started (Day 14, 15, 16). Three of the subjects in GEN 1200mg had multiple crashes during a baseline drive. Sponsor table 16 provides detailed characteristics of subjects with multiple crashes.

**Table 16 Characteristics of Subjects with Multiple Crashes**

		XP13512 1200 mg			XP13512 1800 mg
Subject ID		(b) (6)			
Age/Gender		56/M	49/M	45/F	57/F
Day with Multiple Crashes		16	15	14	16
Other Days with Crashes		14, 15	-1, 14, 16	-1, 1, 15	N/A
ESS	Day -1	24	12	3	19
	Day 14	8	15	2	8
IRLS Rating Scale Score	Day -1	20	22	27	22
	Day 14	22	27	11	18
VAS Alertness (Pre/Post Driving Score)	Day -1 or Day 1 Corresponding to Crash Day	94/88	59/76	100/46	77/52
	Day with Multiple Crashes	88/17	26/29	44/34	81/11
Plasma Gabapentin Level (ng/mL)	Day 14	380	1470	5800	2690
	Day 15	5740	2350	2330	5050
	Day 16	5260	3340	5130	13000

Data Source: DSListing 3, DSListing 17.1, DSListing 18, DSListing 20.2, DSListing 20.3, DSListing 25.2, DSListing 25.3, DSListing 25.4, and DSListing 26.

All four subjects presented in sponsor Table 16, had multiple crashes while on treatment. All three subjects on GEN 1200mg, experienced crashes during other simulated driving assessments, as well. . Two of the three subjects on GEN 1200mg experienced baseline crashes. However, the number of crashes these subjects experienced at baseline was less than while on treatment. Similar to Study, RXP114111, *Simulated driving in Healthy Volunteers on GEN 600mg*, there was an association between SV and crashes (increase in SV during the epoch in which a subject experienced crashes) but there was no association with LPV.

Two subjects (b) (6) in GEN 1200mg cohort, and (b) (6) in GEN 1800mg cohort) had multiple crashes on Day 16 (driving assessment occurred at Tmax). These two subjects also had the largest change in VAS pre versus post driving, (88 versus 17, and 81 versus 11, respectively). For subject (b) (6) in GEN 1800mg cohort, the plasma gabapentin level was the highest and for subject (b) (6) in GEN 1200mg cohort, the plasma gabapentin level was near the highest level. There was no apparent correlation between VAS score, plasma gabapentin levels or crashes for other two subjects (b) (6) both in GEN 1200mg cohort) for driving assessments on Day 14 and Day 15, respectively. Of note, three of the four subjects ( (b) (6) in GEN 1200mg cohort, and (b) (6) in 1800mg cohort) with multiple crashes had lower Epworth Sleepiness Score (ESS) on Day 14, than at baseline.

**VAS**

In study XP083, the VAS change from baseline to Day 15 is shown in Sponsor Table 19.

**Table 19 Alertness VAS at Baseline (Day 1) and Day 15, and Change from Baseline (Day 1) to Day 15 in the Alertness VAS (MITT Population)**

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH <sup>c</sup>	95% CI for Mean	ANOVA Results <sup>a</sup>	
	N=33 <sup>b</sup>	N=28	N=33	N=28		LS Mean (SEM)	95% CI for LS Mean
<b>Baseline (Day 1) Pre-Drive</b>							
Mean (SD)	57.9 (17.12)	65.6 (19.57)	55.3 (25.46)	63.2 (23.39)			
<b>Baseline (Day 1) Post-Drive</b>							
Mean (SD)	47.8 (19.64)	57.0 (27.33)	42.9 (22.14)	52.7 (25.07)			
<b>Day 15 Pre-Drive</b>							
Mean (SD)	59.4 (16.55)	65.6 (24.68)	62.5 (23.75)	63.6 (16.98)			
<b>Day 15 Post-Drive</b>							
Mean (SD)	44.7 (22.59)	50.8 (31.21)	47.5 (26.49)	48.8 (25.41)			
<b>Change from Baseline to Day 15 Pre-Drive</b>							
Mean (SD)	1.5 (15.56)	0.2 (26.98)	7.2 (21.53)	0.4 (22.10)			
XP13512 1200 mg – Pbo					-12.4, 9.8	-0.9 (5.65)	-12.1, 10.2
XP13512 1800 mg – Pbo					-3.6, 14.9	6.1 (5.35)	-4.6, 16.7
<b>Change from Baseline to Day 15 Post-Drive</b>							
Mean (SD)	-3.2 (18.92)	-6.1 (28.44)	4.8 (21.08)	-3.1 (22.97)			
XP13512 1200 mg – Pbo					-15.2, 9.4	-3.6 (5.95)	-15.4, 8.2
XP13512 1800 mg – Pbo					-2.0, 17.9	7.5 (5.68)	-3.7, 18.8
<b>Change from Baseline to Day 15 Post-Drive – Pre-Drive</b>							
Mean (SD)	-4.7 (22.22)	-6.3 (24.55)	-2.2 (27.45)	-3.7 (33.84)			
XP13512 1200 mg – Pbo					-13.7, 10.5	-2.7 (7.01)	-16.6, 11.2
XP13512 1800 mg – Pbo					-9.9, 14.8	1.6 (6.69)	-11.6, 14.9

Data Source: DStable 8.1

a. Least-squares means, standard errors, and 95% confidence intervals were from an ANOVA model with treatment and pooled site as explanatory factors.

b. Pbo/DPH group received diphenhydramine on Day 16 only.

The mean change in VAS score for subjects in GEN 1200mg cohort show they are less alert pre-versus post simulated drive on Day 15. However the mean change in VAS score for subjects in GEN 1800mg cohort show subjects to be only slightly less alert on Day 15.

In study XP083, the VAS change from baseline to Day 16 is shown in Sponsor Table 20.

**Table 20 Alertness VAS at Baseline (Day -1) and Day 16, and Change from Baseline (Day -1) to Day 16 in the Alertness VAS (MITT Population)**

					ANOVA Results <sup>a</sup>		
	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH <sup>c</sup>	95% CI for Mean	LS-Mean (SEM)	95% CI for LS Mean
	N=33 <sup>b</sup>	N=28	N=33	N=28			
<b>Baseline (Day -1) Pre-Drive</b>							
Mean (SD)	58.1 (23.95)	69.0 (24.38)	64.1 (20.34)	73.0 (18.68)			
<b>Baseline (Day -1) Post-Drive</b>							
Mean (SD)	41.5 (24.81)	56.4 (26.66)	47.5 (22.03)	52.4 (25.80)			
<b>Day 16 Pre-Drive</b>							
Mean (SD)	65.1 (17.46)	69.8 (25.76)	55.3 (24.90)	61.3 (22.20)			
<b>Day 16 Post-Drive</b>							
Mean (SD)	55.4 (19.07)	52.7 (29.02)	40.1 (28.46)	38.3 (25.16)			
<b>Change from Baseline to Day 16 Pre-Drive</b>							
Mean (SD)	6.3 (23.44)	0.8 (32.79)	-8.8 (27.61)	-11.8 (24.00)			
XP13512 1200 mg - Pbo					-20.0, 9.2	-6.2 (7.07)	-20.3, 7.8
XP13512 1800 mg - Pbo					-27.7, -2.3	-15.4 (6.76)	-28.8, -2.0
Pbo/DPH - Pbo					-30.3, -5.7	-18.3 (7.04)	-32.3, -4.4
XP13512 1200 mg - Pbo/DPH					-2.8, 28.0	12.1 (7.26)	-2.3, 26.5
XP13512 1800 mg - Pbo/DPH					-10.14, 16.3	2.9 (6.97)	-10.9, 16.7
<b>Change from Baseline to Day 16 Post-Drive</b>							
Mean (SD)	14.3 (22.23)	-3.6 (32.01)	-7.5 (26.17)	-14.0 (29.25)			
XP13512 1200 mg - Pbo					-32.2, -3.7	-16.8 (7.16)	-31.0, -2.6
XP13512 1800 mg - Pbo					-33.9, -9.6	-20.7 (6.85)	-34.2, -7.1
Pbo/DPH - Pbo					-41.8, -14.9	-27.4 (7.13)	-41.5, -13.3
XP13512 1200 mg - Pbo/DPH					-6.0, 26.8	10.6 (7.30)	-3.8, 25.1
XP13512 1800 mg - Pbo/DPH					-7.6, 20.8	6.7 (7.01)	-7.2, 20.6

					ANOVA Results <sup>a</sup>		
	Pbo <sup>b</sup>	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH <sup>c</sup>	95% CI for Mean	LS Mean (SEM)	95% CI for LS-Mean
	N=33	N=28	N=33	N=28			
<b>Change from Baseline to Day 16 Post-Drive - Pre-Drive</b>							
Mean (SD)	7.7 (22.38)	-4.5 (36.14)	1.3 (34.13)	-2.3 (23.91)			
XP13512 1200 mg - Pbo					-27.6, 3.4	-10.3 (7.74)	-25.6, 5.1
XP13512 1800 mg - Pbo					-20.9, 8.1	-5.0 (7.40)	-19.6, 9.7
Pbo/DPH - Pbo					-22.0, 2.1	-8.8 (7.71)	-24.0, 6.5
XP13512 1200 mg - Pbo/DPH					-18.6, 14.2	-1.5 (7.89)	-17.1, 14.1
XP13512 1800 mg - Pbo/DPH					-11.8, 19.0	3.8 (7.57)	-11.2, 18.8

Data Source: DSTable 8.1

- a. Least-squares means, standard errors, and 95% confidence intervals were from an ANOVA model with treatment and pooled site as explanatory factors.
- b. Pre-drive values for the placebo group included only 32 subjects. Post-drive and post-drive - pre-drive values for the placebo group included only 31 subjects.
- c. Pbo/DPH were received at baseline and on Day 16 only.

The mean change in VAS score for subjects in GEN 1200mg cohort show they are less alert pre versus post simulated drive on Day 16, while subjects in GEN 1800mg cohort show that they are more alert on Day 16. The subjects in GEN 1800mg cohort perceive themselves to be more alert on average, than subjects in all other cohorts, including placebo.

**REVIEWER COMMENT:**

The results of the VAS score taken together with the results of change in ESS at Day 14, suggest that the level of alertness/somnolence, is not correlated with driving impairment (crashes). Another possible explanation is that subjects are not aware of their level of

alertness/somnolence that is they are not able to objectively evaluate their level of alertness. The inability to judge one's level of alertness may affect one's ability to drive.

## **DISCUSSION:**

The results of study XP083 are difficult to interpret because of the lack of what appears to be an inverse dose response for the 1800 mg dose compared to the 1200 dose driving performance parameters. Overall, the GEN 1200mg cohort performed more poorly than any of the other cohorts including GEN 1800mg. In terms of simulated crashes, both GEN 1200mg and 1800mg cohorts experienced more simulated crashes including multiple crashes than either placebo or DPH.

In the current submission for Driving Study RXP114111, the sponsor has conducted a study to assess the effect of treatment of GEN 600mg a day, on simulated driving. The primary endpoint, change in LPV from baseline, showed a statistically significant difference for the active control DPH, during the evening simulated driving time point only. There was no statistically significant change in LPV from baseline, for GEN treatment period at any time point. However, there were a greater number of simulated crashes in both the GEN and DPH treatment periods. Although more overall crashes occurred during DPH treatment period, in the evening time point (around Tmax), there was an equal number of subjects in GEN and DPH treatment period, with crashes the next day at the midday time point. All of the crashes in the GEN treatment period occurred the next day, morning (1 crash) and midday time points (3 crashes). Although change in LPV is the primary endpoint of the study, it may not be the most sensitive measure for ability to drive safely. The only correlation between LPV and crashes occurred during the DPH treatment period and evening drive. One could argue that change in LPV showed assay sensitivity; however, it does not explain the lack of correlation between LPV and crashes during the DPH treatment period and midday drive. There appears to be an association between speed variability and crashes across treatment periods as well as among studies.

Study RXP114111, was conducted in healthy volunteers, and therefore the results could may be least applicable to patients with RLS, because the healthy subjects are significantly younger and are not suffering from RLS a sleep disorder that causes insomnia. The mean age of the subjects in the current study is approximately 10-15 years younger than the RLS population. It has been shown that driving performance changes with aging. Elderly drivers perform more poorly on simulated driving, and have reduced reaction time, than younger drivers (Belanger et al *Accid Anal Prev*, 2010). In addition, as seen in study XP088, subjects with RLS have more crashes.

Secondly, the incidence and magnitude of somnolence is higher in subjects with RLS with and without treatment with GEN. As seen in study XP088, VAS scores are lower (less alert) in subjects with RLS compared to healthy volunteers, pre and post simulated driving. Subjects with RLS have a higher incidence of reported somnolence and sedation, when treated with GEN, compared to healthy volunteers or patients other diseases, such as post-herpetic neuralgia (PHN).

During clinical development of GEN for RLS, specifically in the pivotal trials (XP052 and XP053) as well as supportive trial XP081, RLS subjects experienced dose related somnolence and sedation. As seen in Sponsor Table 47, even at 600mg a day, 20% of subjects with RLS experienced somnolence.

**Table 47 Characteristics of Somnolence/ Sedation TEAEs Combined (Safety Population: 12-Week Placebo-Controlled RLS Studies)**

Preferred Term	Number (%) of Subjects					
	Placebo (N=245)	XP13512 600mg (N=163)	XP13512 1200mg (N=269)	XP13512 1800mg (N=38)	XP13512 2400mg (N=45)	XP13512 All Doses (N=515)
<b>Somnolence</b>						
Number of subjects	12 (5)	32 (20)	61 (23)	10 (26)	23 (51)	126 (24)
Number of events	13	37	66	11	30	144
<b>Sedation</b>						
Number of subjects	3 (1)	1 (<1)	11 (4)	3 (8)	3 (7)	18 (3)
Number of events	3	1	15	3	4	23
<b>Any event (somnolence and/or sedation)</b>						
Number of subjects	15 (6)	33 (20)	72 (27)	12 (32)	26 (58)	143 (28)
Number of events	16	38	81	14	34	167
Treatment-related	15 (100)	31 (94)	68 (94)	12 (100)	26 (100)	137 (96)
Leading to dose reduction	1 (7)	1 (3)	16 (22)	1 (8)	7 (27)	25 (17)
Leading to interruption in study medication	0	0	1 (<1)	0	0	1 (<1)
Leading to withdrawal	0	4 (12)	5 (7)	0	2 (8)	11 (8)
Severe	0	3 (9)	3 (4)	0	1 (4)	7 (5)

Data Source: Table 2.84, Table 2.14

Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

The median time to first occurrence of somnolence was 4 days and the majority of subjects taking GEN (all dose groups) reported first occurrence  $\leq 14$  days after starting treatment. The median duration of somnolence, (time to recovery from adverse event of somnolence) was 16 days. Somnolence/sedation was the leading cause of withdrawal for treatment emergent adverse event. The overall rate of withdrawal for somnolence/sedation was 8% (all doses) with the highest rate, 12%, for subjects taking 600mg a day.

There is a higher incidence of somnolence/sedation, in subjects with RLS taking GEN than subjects with other disorders. In pivotal trials using GEN for the treatment of PHN, higher doses were used. The demographic results for the study are shown in sponsor table 9.

**Table 9 Summary of Demographic Characteristics (ITT, PXN110748)**

	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 <sup>[1]</sup>	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)

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

The incidence of somnolence was significantly lower despite the higher doses and increased age of the treatment population (sponsor table 35).

**Table 35 Summary of Dizziness and Somnolence Treatment-Emergent Adverse Events (Safety Population, PXN110748)**

Preferred Term		Number (%) of Subjects			
		PBO- N = 95	GEn 1200 mg N = 107	GEn 2400 mg N = 82	GEn 3600 mg N = 87
Dizziness		14 (15)	18 (17)	21 (26)	26 (30)
	Mild/Mod/Severe (%)	79/21/0	78/11/6 <sup>1</sup>	81/14/5	81/12/8
	Mean Duration (days) <sup>2</sup>	11.3	8.1	18.2	16.3
	Median Duration (days) <sup>2</sup>	3.0	3.0	10.0	3.0
	Mean time (days) to onset	13.1	10.4	16.9	10.9
	Median time (days) to onset	9.0	4.5	4.0	5.0
Somnolence		8 (8)	11 (10)	9 (11)	12 (14)
	Mild/Mod/Severe (%)	50/38/13	55/45/0	56/44/0	75/8/17
	Mean Duration (days) <sup>2</sup>	54.1	32.7	59.6	25.1
	Median Duration (days) <sup>2</sup>	63.5	14.5	72.0	12.5
	Mean time (days) to onset	13.0	9.7	3.3	16.0
	Median time (days) to onset	5.5	5.0	2.0	5.5

In sponsor Table 34, adverse events reported in at least 5% of GEn all dose groups, is shown by age group. Even at the highest doses of GEn, 3600mg, the incidence of somnolence for subjects > 75 was only 1%.

**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)
<b>Preferred Term</b>															
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

Although there was no clear correlation between somnolence as scored by VAS score, and simulated driving in healthy volunteers, the VAS may not be the most appropriate measurement of somnolence. The scale is subjective and, subjects often lack insight into their state of alertness. In addition, subjects with RLS have impaired sleep, hence the classification as a sleep disorder, and appear to have increased rate of somnolence compared to other populations taking GEN.

**ADDENDUM: TCON with Sponsor 10/31/2012**

On October 31, 2012 a teleconference was held with the sponsor in regards to the sNDA, PMR 1588-7, supplement 5. The sponsor was informed that they had fulfilled PMR 1588-7. (b) (4)

(b) (4)

(b) (4)

Although there was no statistically significant difference in the primary endpoint, change from baseline in mean LPV between treatment periods, there were an increased number of crashes during GEN and DPH treatment periods as compared to placebo treatment period. The number of subjects who crashed while on GEN was similar to treatment with DPH, both at Tmax and next day. (REVIEWER TABLE)

**REVIEWER TABLE: Simulated Crashes at Evaluated Timepoints (Secondary Measure)**

<b>Simulated Driving Timepoint and Hours Post Dose</b>	<b>Baseline N = 36 n (%)</b>	<b>Placebo N = 36 n (%)</b>	<b>HORIZANT 600 mg N = 35 n (%)</b>	<b>Diphenhydramine 50 mg N = 36 n (%)</b>
<b>Day 5</b> Evening (7 to 9pm) 2 to 4 hours post dose	0 (0)	0 (0)	0 (0)	3 (9)
<b>Day 6</b> Morning (7 to 9am) 14 to 16 hours post dose	2 (6)	1 (3)	1 (3)	0 (0)
<b>Day 6</b> Midday (11am to 1pm) 18 to 20 hours post dose	1 (3)	0 (0)	3 (9)	3 (8)

As stated previously in this review (as well as in sponsor comments), subjects with RLS are more likely to experience crashes, particularly the next day (even without treatment) compared to healthy volunteers (study XP088). In addition, subjects with RLS who were treated with GEN 1200mg or 1800mg experienced increased number of crashes, as well as an increase in LPV, at Tmax as compared to placebo (study XP083).

The sponsor did not agree with the Agency’s interpretation of the study results and submitted a response in writing (11/12/2012) to the Agency. The sponsor responded by ISSUES discussed during the teleconference with the Agency. These ISSUES are outlined below.

**ISSUE 1: Applicability of Healthy Subjects as a Proxy for Patients with RLS in a Simulated Driving Study**

- Subjects with RLS performed similarly to healthy volunteers on simulated driving as shown in study XP088. The LPV, speed variability and brake reaction time were similar for the two groups. In addition, the sponsor states that the overall incidence of crashes was 13% for both groups.
- Incidence of somnolence and sedation was similar between healthy volunteers and patients with RLS.

- Difference in mean age between healthy volunteers and patients with RLS is approximately 17 years. However both cohorts fall into a range where driving ability is not expected to be different.
- In study XP088, subjects with RLS reported lower VAS alertness scores, longer time to fall asleep and shorter total sleep time when compared to healthy volunteers. Despite these findings, the Epworth Sleepiness Scale (ESS) scores were not abnormally high amongst subjects with RLS (mean 8.9 at screening), suggesting subjects with RLS may be hypervigilant compared to healthy volunteers.

**REVIEWER COMMENT:** Although the number of subjects who crashed was similar for the two groups in study XP088, all of the crashes occurred the next day for the subjects with RLS as compared to healthy volunteers. In the Clinical Study Report (CSR), the sponsor states “Within group comparisons between the afternoon (Day1) and the morning (Day2) driving tests showed that RLS subjects had crashes at Epochs 5 and 6 in the morning (Day 2) test; whereas, normal subjects had crashes at Epochs 3 and 5 in the afternoon (Day 1) test”.... The worsening of driving performance in later epochs of the test observed in these RLS individuals is typically seen in subjects with sleep disorders or sleep deprivation and suggests that sleep disturbance caused by RLS may affect driving performance...”

A similar ‘pattern’ of crashes was noted in study XP083; patients with RLS had increased number of crashes, not only at Tmax, but also the following morning when treated with GEn as compared to placebo.

In addition, there is evidence suggesting that insomnia and treatment with anticonvulsant medications increase the risk for real motor vehicle crashes (MVC) the National Highway Transportation Safety Administration (NHTSA), using proprietary and non-proprietary databases, performed a case control analysis for the risk of MVC. The study results showed an increased risk for real crashes for patients with insomnia and age 50 or older (OR-3.16[C.I. =1.69-5.12]. Restless Legs Syndrome is classified as a sleep related movement disorder associated with insomnia. Anticonvulsant drugs are also associated with an increased risk for MVC OR=1.97 [C.I. = 1.64-2.38] in adults age 50 and older. The age of the subjects in this epidemiological study is most relevant to the population likely to suffer from RLS and the segment of the population most likely to use Horizant. This is in distinct contrast to the population studied in study RXP114111 that included healthy volunteers mean age 36 years.

## **ISSUE 2: Relevance of Simulated Crashes in GSK and Xenoport Sponsored Simulated Driving Studies**

- Incidence of simulated crashes in subjects administered 600mg GEn (8.6%) is within background incidence of simulated crashes in GSK and Xenoport conducted simulated driving studies, as well as those in the literature.
- In studies RXP114111 and XP083, simulated crashes are unrelated to drug pharmacodynamics and do indicate a [safety] signal.

- The occurrence of simulated crashes has not been shown to be an accurate predictor of whether a subject will crash a motor vehicle in real life setting due to greater sensitivity of the driving simulator paradigm.
- Simulated crashes are not a valuable indicator of driving performance and do not predict on-road crashes.

**REVIEWER COMMENT:**

Although lateral lane position variability (LPV) is commonly used in on-road as well as simulated driving studies, crashes are often used as primary endpoints as well. The increased number of subjects with crashes during GEN treatment period in study RXP114111, although small, is of concern. However, of possibly greater significance is the timing of crashes. In both study RXP114111 and study XP083, there are an increased number of subjects who crash the morning (and afternoon) following treatment with GEN. In study XP083, there is an increase number of subjects with crashes on Day 15 (see table) in GEN 1200mg cohort compared to placebo.

<b>Simulated Driving Timepoint</b>	<b>Placebo N=33</b> Number of subjects with crashes (%)	<b>XP13152 1200mg</b> N=28 Number of subjects with crashes (%)	<b>XP13152 1800mg</b> N=33 Number of subjects with crashes (%)	<b>Placebo/DPH 50mg (Day 16 only)</b> N=28 Number of subjects with crashes (%)
<b>Baseline evening (7-9pm)</b>	3(9)	6(21.4)	3(9.1)	2(7.1)
<b>Baseline morning (7-9am)</b>	1(3.1)	4(14.3)	3(9.4)	3(11.1)
<b>Day 14 (7-9pm) 2-4 hours post dose</b>	4(12.1)	6(21.4)	1(3.0)	1(3.6)
<b>Day 15 (7-9am) 14-16 hours post dose</b>	1(3.0)	10(35.7)	1(3.2)	0(0)
<b>Day 16 (5-6pm) GEN/PBO dosed at 11am, DPH dosed at 5pm, Tmax</b>	0(0)	8(28.6)	6(18.2)	3(10.7)

The sponsor states that crashes are unrelated to the pharmacodynamic effects of GEN. In study XP083 on Day 16 (Tmax) there is an increased number of subjects who crash in GEN 1200mg and 1800mg cohorts compared to placebo. In the current simulated driving study, RXP114111, simulated driving was not tested at Tmax. It appears that crashes associated with the pharmacodynamics effects of GEN and they occur at times unrelated to peak plasma concentrations of the GEN. In the current study, RXP114111, this pattern is seen with DPH as well. On Day 5 evening drive (Tmax for DPH); there are an increased number of subjects with crashes. The same number of subjects also crash on Day 6, afternoon drive, 18-20 hours post dosing DPH.

In addition, the sponsor states that the request for additional driving studies is "...scientifically and procedurally inappropriate..., for the following reasons:

- The current label for HORIZANT contains a driving warning that is more severe than other drugs used to treat patients with RLS
- Dopamine agonists, which are the most prescribed treatment for RLS, have product labels that report patients falling asleep while driving motor vehicles when taking these agents
- Generic gabapentin, prescribed off-label for the treatment of RLS, contains a precaution that instructs prescribers to advise patients that they should not drive a car nor operate other complex machinery until they have gained sufficient experience to gauge any drug effect
- The sponsor states that they are unaware of any initiatives to systematically evaluate driving performance following administration of a dopamine agonist or gabapentin, in the same manner that is being requested for Horizant.

#### REVIEWER COMMENT:

Similar to the label for Horizant, the current labeling for dopamine agonists (Mirapex, Requip) include detailed information about driving and somnolence. These labels also underscore the fact that patients with the diseases such as Parkinson's disease (PD) as well as Restless Leg Syndrome (RLS) have a higher incidence of somnolence while taking these medications and therefore are at increased risk for falling asleep while performing activities such as driving. These symptoms may occur as far out as one year after initiating treatment. In addition, patients with PD and/or RLS may not acknowledge that they are somnolent.

**WARNINGS Falling Asleep During Activities of Daily Living: Patients treated with REQUIP have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on REQUIP, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as 1 year after initiation of treatment.**

**In controlled clinical trials, somnolence was a common occurrence in patients receiving REQUIP and is more frequent in Parkinson's disease (up to 40% REQUIP,**

**6% placebo) than in Restless Legs Syndrome (12% REQUIP, 6% placebo). Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.**

**Before initiating treatment with REQUIP, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with REQUIP such as concomitant sedating medications, the presence of sleep disorders (other than Restless Legs Syndrome), and concomitant medications that increase ropinirole plasma levels (e.g., ciprofloxacin—see PRECAUTIONS: Drug Interactions). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), REQUIP should ordinarily be discontinued. (See DOSAGE AND ADMINISTRATION for guidance in discontinuing REQUIP.) If a decision is made to continue REQUIP, patients should be advised to not drive and to avoid other potentially dangerous activities. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.**

## **DISCUSSION:**

The study results from RXP114111 do not show a statistically significant difference for the primary endpoint, change in mean LPV. However, the study was not powered to demonstrate a statistically significant effect on LPV at times other than Tmax and only for the active control, DPH. The secondary endpoint as set by the sponsor, crashes do, in the opinion of the reviewer, show a possible safety signal. Although not statistically significant, the study was not powered to show a difference in number/rate of crashes between placebo and GEN. Overall, the number of subjects who crash is higher in both GEN and DPH treatment periods compared to placebo. Taken together with the previous driving study XP083, there appears to be an increased number of crashes particularly at Tmax and the morning and after taking GEN

(b) (4)

(b) (4)

## **FDA MEETING PACKAGE (February 5, 2013)**

On (DATE) the sponsor requested a face to face meeting with the Agency. The meeting was granted and scheduled for March 5, 2013. The sponsor submitted a Briefing Package February 5, 2013. The briefing package included detailed presentations of XenoPort's

objections to the PMR proposal

(b) (4)

(b) (4)

- **Study RXP114111 Did Not Indicate a Safety Signal**

- The sponsor stated that the primary outcome of the study, change from baseline in LPV, showed a statistically significant difference for the active control, DPH, but not for GEN compared to placebo. In addition, the sponsor argues that SDLP is a validated measure of the driver's control of the vehicle and has been use to predict the risk for real world accidents. The sponsor supported their argument showing crash data for subjects taking alcohol. However, the correlation between crashes and alcohol were seen in subjects with blood alcohol levels known to cause accidents.
- During a review of the briefing package, the division noted that the definition of crashes did not necessarily take into account the possibility for crossing over the centerline (lane crossings), into the opposite lane of traffic. The sponsor included a post-hoc analysis of lane crossings as requested by the division.

**FDA Question:**

*What is recorded by the software program, if the subject vehicle edge crosses the center dividing line to a distance that would meet the perimeter of an oncoming vehicle but there is no oncoming at the time of the lane crossing (only 1 auto pass in the opposing lane every 10 minutes)? If lane crossing is not recorded as a crash please recalculate the data to record "potential crashes" as anytime the subject's vehicle edge crosses the center divider or right edge (beyond + 13 ft. or -13 ft.). Evaluate the entire test time not just the 1 minute window surrounding a crash. Provide the total number of potential crashes, mean, median, outlier analysis for each treatment group for each test time. Provide the information for the baseline and change from baseline for each parameter as well. Construct a model that includes the baseline number of simulated crashes and compare the results for each treatment group for each test time. If this is not feasible please explain why.*

In response to the request the sponsor provided the following data table (Sponsor Table 7).

**Table 7. Number of Subjects with Out of Lane LP Values (LP<0 or LP>13 feet) and Total Time Spent Out of Lane**

Treatment	Time of Evaluation	Number (%) of Subjects Out of Lane (LP<0 or LP>13)	Total Number of One Second Time points Out of Lane* (LP<0 or LP>13)
None (baseline) (N = 36)	Day 5 Evening	2 (6%)	3
	Day 6 Morning	3 (8%)	14
	Day 6 Midday	3 (8%)	5
Placebo (N = 36)	Day 5 Evening	3 (8%)	3
	Day 6 Morning	6 (17%)	23
	Day 6 Midday	3 (8%)	6
DPH 50 mg (N = 36)	Day 5 Evening	10 (28%)	89
	Day 6 Morning	7 (19%)	34
	Day 6 Midday	7 (19%)	37
Gabapentin Enacarbil 600 mg (N = 35)	Day 5 Evening	4 (11%)	46
	Day 6 Morning	7 (20%)	31
	Day 6 Midday	6 (17%)	25

\*Total calculated from summation of all time points and subjects.

The sponsor argues that the number of one-second time points out of lane is not a validated measure of driving performance and may not reflect impairment, due to the subjective selection of preferred driving position.

**REVIEWER COMMENT:**

SDLP or LPV is not the only parameter that is useful to evaluate the effects of medications on simulated driving performance. There is no standard method of simulated or on-road driving assessment that is accepted as a “Gold Standard” for the evaluation of the effects of medications on driving. The report from the National Highway Traffic Safety Administration (NHTSA) March 2011 on Drugged Driving highlights a need for a standardized evaluation of drug effects on driving. Multiple factors including encroachment beyond traffic control boundaries are important. Study RXP114111 was designed to detect a statistically significant difference for mean change in SDLPV between treatment groups. Although the mean change in SDLPV was not statistically significant, the findings for other safety endpoints are not dismissible. Other parameters, such as speed variability, crashes, absolute lateral lane position and lane crossings are also important to consider when assessing simulated driving studies.

In the simulated driving scenario, a subject would have to cross completely to the opposite side (>13 feet), or hit an oncoming car that passed once every ten minutes, in order to be considered a crash. However, in an on-road scenario, crossing over the center lane (lane crossings) into on-coming traffic would theoretically cause a crash. Therefore,

the division requested that sponsor calculate all lane crossings, which could be considered potential crashes.

In study RXP114111, the lateral lane position (as shown in sponsor Table 7 from briefing package) was variable for GEN and DPH group at all driving points compared to baseline and placebo. The greatest percentage of subjects outside of lane position was Day 5 evening drive (28%) for the DPH group. For GEN group the greatest percentage of subjects outside of lane position was Day 6 morning drive (20%) followed by Day 6 midday drive (17%). The percentage of subjects outside of lane position for GEN and DPH groups was greater than all driving time points for baseline (6,8,8%) and all but the midday driving time point for placebo (8,17,8%). The results for time spent out of lane indicate GEN most closely resembles the results for DPH (active control) on day 6. As stated previously there is a consistent pattern of increased crashes and line crossings in the GEN and DPH groups midday driving. In addition, there are increased crashes, line crossings and LPV in DPH treatment group at Tmax, evening driving (positive control). GEN was not tested at Tmax and therefore it is not known what effect would have been seen on LPV, crashes and line crossings at this time point.

However, on review of individual subjects who crashed, there was not a consistent correlation between subjects with increased number of lane crossings and crashes. In other words, the timing and treatment period for lane crossings and crashes was similar when looking at the data as a whole, but on an individual, subject, level there was no correlation between lane crossings and crashes.

- **Study RXP114111 Did Not Provide a “New” Safety Signal**
  - The sponsor believes that it is “...inappropriate to characterize such a signal as ‘new’ safety information”, since GEN related driving impairment was already observed in pre-approval study XP083.

**REVIEWER COMMENT:**

Although the sponsor has conducted previous simulated driving studies, pre-approval, this is the first simulated driving study conducted with GEN 600mg. Therefore, the division would consider this new safety information.

- **XenoPort’s Original Conclusion That Healthy Volunteers Are an Adequate Population to Assess Driving Effects of GEN**
  - The sponsor argues that the division agreed to using healthy volunteers for study RXP114111

- There is no significant difference in driving performance for the two populations, healthy volunteers (HV) and patients with RLS as shown in study XP088.

**REVIEWER COMMENT:** The division agreed to use HV in study RXP114111 in order to expedite completion of the study. The Division does not agree that there is no difference in driving performance between healthy volunteers and patients with RLS. The sponsor has noted in CSR for XP088, that there is a difference in driving performance between the two populations which is likely related to the fact that RLS is classified a sleep disorder. Subjects with sleep disorders been shown to have impaired driving performance.

- **The Current Horizant Label Already Provides a Strong Warning**

- The sponsor argues that the label for Horizant contains strong language “significant driving impairment” in the WARNING section. The sponsor believes that this language is adequate to protect the safety of patients as well as inform prescribers of possible risks.

**REVIEWER COMMENT:** Since the study was conducted over 5 days, the sponsor is not able to comment on the possible duration of impairment in driving. However, the division agrees that currently agreed upon label is adequate, if not specific, in warning subjects and prescribers about possible driving impairment.



**REVIEWER COMMENT:** Ideally, the Division would not only like the label to warn patients with RLS, as well as prescribers of the effect of Horizant 600mg on driving, but also on the duration of this impairment. However, the division does recognize the limitations of designing a simulated driving study that would be able to assess both qualitatively as well as quantitatively, the effect of Horizant on driving, in patients with RLS, with the current .level of understanding of simulated driving measurements.



**REVIEWER COMMENT:** The sponsor has not conducted any studies directly comparing exposure of Horizant to gabapentin and/or other gabapentin containing products. In addition, driving impairment is not necessarily related to drug exposure.

Although, there have not been any driving studies conducted with dopamine agonists, the labels for these products are restrictive, to the point of warning patients to stop driving if they feel somnolent.

Ideally a simulated driving study that evaluated several parameters (LPV, crashes, speed variability, lane crossings) over a longer period of time, in subjects with RLS could be beneficial in Horizant labeling. However, given the current knowledge in the field of simulated driving, and the fact that there is no “GOLD STANDARD” agreed upon, it would be extremely difficult to design an appropriate trial. At this point, taking a conservative approach and warning prescribers and patients not to drive if they experience somnolence and or sedation, is most appropriate.

**RECOMMENDATION:**

*Approval of current agreed upon labeling and release of PMR for driving studies.*

**4. Label**

Agreed Upon Language

**14.3 Effects on Driving**

Driving performance was assessed in a three way crossover study in healthy volunteers (mean age 36 years). Subjects were dosed at approximately 5 pm with HORIZANT 600 mg (for five days), diphenhydramine 50 mg (1 dose), and placebo (for five days). After the last dose, driving was evaluated on a computer-based simulation for 1 hour in the evening approximately 2 to 4 hours after dosing (7 to 9 pm), in the morning after dosing (7 to 9 am), and at midday the day after dosing (11 am to 1pm). The primary endpoint of the study was lane position variability. There was no difference in change from baseline in lane position variability for HORIZANT compared to placebo at any of the simulated driving time points. Secondary measures included speed variability and the occurrence of simulated crashes. Subjects in this study experienced simulated crashes as described in Table 7. At the times that simulated crashes occurred, there was an increase in average speed variability in the HORIZANT and diphenhydramine treated groups that were most notable in patients who experienced simulated crashes, but no increases in lane position variability. Later time points post-dosing or the effects of driving after more than five days of dosing with HORIZANT were not evaluated.

**Table 7. Simulated Crashes at Evaluated Timepoints (Secondary Measure)**

<b>Simulated Driving Time point and Hours Post Dose</b>	<b>Baseline N = 36 n (%)</b>	<b>Placebo N = 36 n (%)</b>	<b>HORIZANT 600 mg N = 35 n (%)</b>	<b>Diphenhydramine 50 mg N = 36 n (%)</b>
<b>Day 5</b> Evening (7 to 9pm) 2 to 4 hours post dose	0 (0)	0 (0)	0 (0)	3 (9)
<b>Day 6</b> Morning (7 to 9am) 14 to 16 hours post dose	2 (6)	1 (3)	1 (3)	0 (0)
<b>Day 6</b> Midday (11 am to 1pm) 18 to 20 hours post dose	1 (3)	0 (0)	3 (9)	3 (8)

The results of a separate 2-week driving simulation study in patients (mean age 47 years) with moderate-to-severe primary RLS showed that once daily doses of 1,200 mg and 1,800 mg of HORIZANT significantly impaired simulated driving performance based on lane position variability. An increased number of simulated crashes were reported in patients tested near  $T_{max}$  after receiving 1,200 mg or 1,800 mg of HORIZANT compared to patients treated with diphenhydramine 50 mg. In addition patients receiving 1,200 mg of HORIZANT experienced an increased number of simulated crashes at 14 to 16 hours after dosing compared with placebo, diphenhydramine, and 1,800 mg of HORIZANT.

The design limitations of these two studies do not permit inference regarding dose response relationship or the duration of the effect HORIZANT has on driving in patients with RLS.

The results of a separate driving simulation study comparing untreated RLS patients and healthy subjects showed no difference in lane position variability but an increase in speed variability associated with a greater number of simulated crashes in RLS patients relative to healthy subjects, which may indicate impaired driving in RLS patients in the absence of medication.

### 14.3 Effects on Driving

Driving performance was assessed in a three way crossover study in healthy volunteers (mean age 36 years). Subjects were dosed at approximately 5 pm with HORIZANT 600 mg (for five days), diphenhydramine 50 mg (1 dose), and placebo (for five days). After the last dose, driving was evaluated on a computer-based simulation for 1 hour in the evening approximately 2 to 4 hours after dosing (7 to 9 pm), in the morning after dosing (7 to 9 am), and at midday the day after dosing (11 am to 1pm). The primary endpoint of the study was lane position variability. There was no difference in change from baseline in lane position variability for HORIZANT compared to placebo at any of the simulated driving timepoints. Secondary measures included speed variability and the occurrence of simulated crashes. Subjects in this study experienced simulated crashes as described in Table 7. At the times that simulated crashes occurred, there was an increase in average speed variability in the HORIZANT and diphenhydramine treated groups that were most notable in patients who experienced simulated crashes, but no increases in lane position variability. Later time points post-dosing or the effects of driving after more than five days of dosing with HORIZANT were not evaluated.

5. Table 7. Simulated Crashes at Evaluated Timepoints (Secondary Measure)

Simulated Driving Timepoint and Hours Post Dose	Baseline N = 36 n (%)	Placebo N = 36 n (%)	HORIZANT 600 mg N = 35 n (%)	Diphenhydramine 50 mg N = 36 n (%)
Day 5 Evening (7 to 9pm) 2 to 4 hours post dose	0 (0)	0 (0)	0 (0)	3 (9)
Day 6 Morning (7 to 9am) 14 to 16 hours post dose	2 (6)	1 (3)	1 (3)	0 (0)
Day 6 Midday (11am to 1pm) 18 to 20 hours post dose	1 (3)	0 (0)	3 (9)	3 (8)

The results of a separate 2-week driving simulation study in patients (mean age 47 years) with moderate-to-severe primary RLS showed that once daily doses of 1,200 mg and 1,800 mg of HORIZANT significantly impaired simulated driving performance based on lane position variability. An increased number of simulated crashes were reported in patients tested near  $T_{max}$  after receiving 1,200 mg or 1,800 mg of HORIZANT compared to patients treated with diphenhydramine 50 mg. In addition patients receiving 1,200 mg of HORIZANT experienced an increased number of simulated crashes at 14 to 16 hours after dosing compared with placebo, diphenhydramine, and 1,800 mg of HORIZANT.

The design limitations of these two studies do not permit inference regarding dose response relationship or the duration of the effect HORIZANT has on driving in patients with RLS.

The results of a separate driving simulation study comparing untreated RLS patients and healthy subjects showed no difference in lane position variability but an increase in speed variability associated with a greater number of simulated crashes in RLS patients relative to healthy subjects, which may indicate impaired driving in RLS patients in the absence of medication.

Susanne R. Goldstein, MD  
Medical Reviewer – DNDP ODE I

cc:  
HFD-120

APPEARS THIS WAY ON ORIGINAL

## REFERENCES

1. Verster JC, Roth T. Standard operation procedures for conducting the on-the-road driving test, and measurement of the standard deviation of lateral position (SDLP). *International Journal of General Medicine*. 2011;(4) 359–371.
2. Verster JC, Roth T. Drivers Can Poorly Predict Their Own Driving Impairment: A Comparison Between Measurements of Subjective and Objective Driving Quality. *Psychopharmacology*. 2012;(219) 775-781.
3. Peterson, BL. Prevalence of Gabapentin in Impaired Driving Cases in Washington State in 2003-2007. *J of Analytical Tox*. 2009;(33) 545-549.
4. Philip, P et al. Fatigue, Sleepiness, and Performance in Simulated Versus Real Driving Conditions. *Sleep*. 2005;28(12) 1511-1516.
5. Moller, HJ et al. Simulator Performance, Microsleep episodes, and Subjective Sleepiness: Normative Data Using Convergent Methodologies to Assess Driver Drowsiness. *J of Psychosomatic Res*. 2006;(61) 335-342.
6. Savino, MR. Standardized Names and Definitions for Driving Performance Measures. Masters Thesis, Human Factors Engineering, Tufts University. 2009.
7. Pizza, F et al. Daytime Driving Simulation Performance and Sleepiness in Obstructive Sleep Apnoea Patients. *Acc Analysis & Prev*. 2008 (40) 602-609.
8. Bocca, ML et al. Zolpidem and Zopiclone Impair Similarly Monotonous Driving Performance After a Single Nighttime Intake in Aged Subjects. *Psychopharmacology*. 2011 (214) 699-706.
9. U.S. Department of Transportation National Highway Traffic Safety Administration. Drugged Driving Expert Panel Report: A Consensus Protocol for Assessing the Potential of Drugs to Impair Driving. March 2011
10. U.S. Department of Transportation National Highway Traffic Safety Administration. Drugs and Human Performance Fact Sheets April 2004.
11. U.S. Department of Transportation National Highway Traffic Safety Administration, Multiple Medications and Vehicle Crashes: Analysis of Databases, Final Report. May 2008

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

/s/  
-----

SUSANNE R GOLDSTEIN  
03/14/2013

GERALD D PODSKALNY  
03/14/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022399Orig1s005**

**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

### CLINICAL STUDIES

**NDA/BLA Serial Number:** 22399 (0093)

**Drug Name:** Horizant (Gabapentin Enacarbil)

**Indication(s):** Restless Leg Syndrome

**Applicant:** GSK

**Date(s):** PDUFA: December 29, 2012

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics 1

**Statistical Reviewer:** Tristan Massie, Ph.D.

**Concurring Reviewers:** Kun Jin, Ph.D., Team Leader  
Hsien-Ming (James) Hung, Director Division of Biometrics 1

**Medical Division:** Neurology (HFD-120)

**Clinical Team:** Susanne Goldstein, M.D., Medical Reviewer  
Gerald Podskalny, M.D., Team Leader  
Russell Katz, M.D., Director

**Project Manager:** Fannie Choy

**Keywords:** Driving Safety; Healthy Study Population; Extrapolation/Bridging

# Table of Contents

<b>STATISTICAL REVIEW AND EVALUATION .....</b>	<b>1</b>
<b>LIST OF TABLES.....</b>	<b>3</b>
<b>LIST OF FIGURES.....</b>	<b>4</b>
<b>1 EXECUTIVE SUMMARY .....</b>	<b>5</b>
<b>2 INTRODUCTION .....</b>	<b>6</b>
2.1 OVERVIEW.....	6
2.1.1 <i>Background on Previously Reviewed Study XP083</i> .....	8
2.2 DATA SOURCES .....	9
<b>3 STATISTICAL EVALUATION .....</b>	<b>9</b>
3.1 EVALUATION OF EFFICACY .....	9
3.2 EVALUATION OF SAFETY .....	10
3.2.1 <i>RXP114111</i> .....	10
3.2.1.1 Study Design and Analysis Plan .....	10
3.2.1.2 Subject Disposition and Demographic Characteristics.....	16
3.2.1.3 Sponsor’s Results.....	17
3.2.1.4 Reviewer’s Results.....	27
<b>4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....</b>	<b>29</b>
4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION .....	29
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS .....	30
<b>5 SUMMARY AND CONCLUSIONS .....</b>	<b>30</b>
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE .....	30
5.2 CONCLUSIONS AND RECOMMENDATIONS .....	31

## LIST OF TABLES

Table 1 Key Driving Studies .....	7
Table 2 RXP114111 : Subject Disposition and Demographic Characteristics .....	16
Table 3 RXP114111: Change in Lane Position Variability .....	18
Table 4 RXP114111: Large Changes in Lane Position Variability (ITT Population) .....	20
Table 5 RXP114111: Change in Speed Variability (mph) (ITT Population) .....	22
Table 6 RXP114111 Number and Percentage of Subjects with Simulated Driving Crashes (ITT Population) .....	23
Table 7 Study XP088 Number of Crashes by Study Group .....	24
Table 8 RXP114111: Alertness Visual Analogue Scale .....	26

## LIST OF FIGURES

Figure 1 Subject Profiles of Standard Deviation of Linear Position (LPV) by Assigned Treatment Sequence (Day 6 Morning).....	28
Figure 2 Subject Profiles of Change in VAS Post-Test from Baseline by Assigned Treatment Sequence (Day 6 Morning).....	29

## 1 EXECUTIVE SUMMARY

An earlier parallel group driving safety study, XP083, using 1200 mg and 1800 mg Gabapentin Encarbil doses, higher than the recommended dose for restless leg syndrome, as well as diphenhydramine 50 mg showed some statistically significant effects on driving safety of these doses compared to placebo. However, the lower dose surprisingly showed more consistent effects in that study and even the low dose used in that study was higher than the recommended dose for the indication of restless leg syndrome associated with the related NDA. Therefore, a post marketing driving safety study was done in a healthy population to investigate the recommended dose for Restless leg syndrome and this latter study is the basis for this supplement. This study which utilized a 3 period, 3 treatment crossover design showed an effect of the active control, Diphenhydramine 50 mg, in the Evening on Day 5 in terms of the primary endpoint, standard deviation of lane position on the road in the simulated driving test, but no significant effects of Gabapentin encarbil compared to placebo at the three scheduled assessment times: Day 5 evening, Day 6 morning and Day 6 Midday on the prespecified driving safety measures. The study demonstrated assay sensitivity of the active control as planned at a different time than an effect would be expected for Gabapentin due to different pharmacokinetic properties of the drugs. However, because it was done in the healthy population it still seems somewhat uncertain whether this recommended dose affects driving safety in the Restless Leg Syndrome population associated with the NDA. Also, the study did not demonstrate equivalence of placebo and Gabapentin rather it failed to detect a significant difference on the primary endpoint, standard deviation of linear position. This does not rule out a smaller (than Diphenhydramine 50 mg) but still important worsening effect of Gabapentin on driving safety compared to placebo, so it does not establish equivalence of Gabapentin and placebo. If feasible an equivalence or noninferiority design would have been more appropriate for a study question such as this since the sponsor's goal was to show "equivalence" to placebo in terms of driving safety. Also, here the question remains is 50 mg diphenhydramine the smallest dose that could have served as the active control, i.e., have the desired safety effect. If not, then we cannot be sure that the absence of an observed significant driving effect of Gabapentin compared to placebo on the primary endpoint isn't still a study power issue. There were numerically more simulated crashes in the Gabapentin group on Day 6 Midday than there were on Placebo at the same time (3 vs. 0). This result was not the primary endpoint and it was not nominally statistically significant but it was almost identical to the crash results for the active control, DPH, on Day 5 Evening which was also not statistically significant. The study may not have been adequately powered to detect an effect on the secondary endpoint of crashes. Despite the lack of statistical significance the trend towards more simulated crashes on Gabapentin than placebo may still be worrisome due to the serious implications for public safety that such an effect would have.

## 2 INTRODUCTION

### 2.1 Overview

Gabapentin enacarbil (GEN; HORIZANT® Extended-Release Tablets) was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults on April 6, 2011 and became commercially available on June 6, 2011 (first shipment), with formal launch on July 1, 2011. The IND under which GEN was developed for RLS is 71352.

Two studies have been conducted in order to assess the effect of GEN on simulated driving performance. Study XP083 was submitted in the original NDA 022399 for moderate-to-severe primary RLS in adults and reviewed then but is summarized briefly below in order to provide background information. Study XP083 was reviewed for Biometrics by Dr. Sharon Yan as part of the original application for the indication in restless legs syndrome. That review is associated with a submit date of 10/10/2009.

Study RXP114111 was recently conducted in healthy volunteers as a Post Marketing Requirement (1588-7).

- RXP114111 assessed the effect of GEN on simulated driving performance and
- The study was conducted at a single center in the United States.

The US Prescribing Information (PI) for HORIZANT, a pro-drug of gabapentin pro-drug, includes a warning about the potential impact on driving ability and advises that patients not drive until they have gained sufficient experience with HORIZANT to assess whether it will impair their ability to drive. The USPI for Neurontin (gabapentin) and Gralise (gabapentin) tablets advises these medications cause symptoms of central nervous system (CNS) depression and although there is no warning with regard to driving both products state that patients should not drive until sufficient experience is gained with their administration [Gralise PI, 2012; Neurontin PI, 2011]. Study RXP114111 was conducted to evaluate the effect of the recommended 600 mg/day dose of GEN in the treatment of moderate-to-severe primary RLS on simulated driving.

RXP114111 was a randomized, double-blind, double-dummy, active- and placebo-controlled, 3-period crossover study designed to assess the effect of gabapentin enacarbil (GEN) 600 mg on simulated driving performance in healthy adult subjects. Each subject participated in 3 dosing (placebo, GEN 600 mg, and diphenhydramine 50 mg) and simulated driving assessment periods. After 5 days of dosing, GEN 600 mg indicated a lack of effect on simulated driving performance in this study. Diphenhydramine 50 mg impaired simulated driving ability on the evening of dosing, demonstrating assay sensitivity.

Table 1 provides some details on the simulated driving safety studies.

**Table 1 Key Driving Studies**

Study Number/ Design/ Dates	# of Subjects per Arm	Follow-up Period	Completer N (%)	Primary Efficacy	Study Populati on
XP088 (Parallel Cohort) 04Dec 2006 to 14Mar2007	N=30 <b>No drug intervention</b>	2 days	100%	Std Dev of Linear Position (LPV) from Simulated Driving Test on day 1, 4PM or day 2, 8 AM	<b>N=15 Healthy, N=15 RLS</b> Single Center in US
XP083 (Parallel group) 09Apr2007 to 09Nov2007	PBO: 34 1200mg: 32 1800mg: 34 PBO/DPH: 30	16 days (Estimated $T_{max}$ for Gabapentin)	PBO: 32 (94%) 1200mg: 28 (88%) 1800mg: 33 (97%) PBO/DPH: 28 (93%)	Change from Baseline in Std Dev of Linear Position for Simulated Driving Test On Day 16	<b>RLS</b> 19 centers in US
RXP114111 (3 Period, 3 Treatment Crossover Study with Placebo, 600mgGeN, DPH 50 mg) 30Jun2011 to 11Oct2011	N=36 GEn 600 mg for 5 days; placebo for 5 days and placebo/diphenhydr amine 50 mg with placebo for 4 days and diphenhydramine on Day 5; Oral ; 3 6-day treatment periods	6 weeks <b>Double Blind:</b> 2 weeks treatment/ 1 week washout/ 2 weeks treatment	97%	Change from Baseline in Standard Deviation of Linear Position in Simulated Driving Test on Day 6 Morning	<b>Healthy Subjects</b> at Single center in US

It seems there was some potential for unblinding of subjects in this study RXP114111 because diphenhydramine is known to be sedating and to have a distinct time of onset of sedative effect compared to the presumed time of onset for Gabapentin enacarbil based on pharmacokinetics (if it too has such an effect). This reviewer isn't aware of any clear evidence of it but if there was such unblinding then it might potentially bias the determination of assay sensitivity in this study.

### 2.1.1 Background on Previously Reviewed Study XP083

This study was a multi-center, randomized, double-blind, active- and placebo-controlled, parallel-group study to assess simulated driving performance in GEN-treated subjects with RLS). Eligible subjects were randomized to receive a once daily dose of placebo (2 groups), GEN 1200 mg, or GEN 1800 mg for 16 days. On Day 16 (estimated Tmax), one of the placebo groups also received one 50 mg dose of diphenhydramine (DPH) to assess the effects of an agent known to have sedative properties, while the other 3 groups received a DPH placebo. Dosing on Days 1 to 14 was at 5 PM. Testing of simulated driving performance took place between 7-9 PM on Day 14 and between 7-9 AM on Day 15 to assess the effects of treatment shortly after dosing and the following morning. Dosing of GEN or matching placebo on Days 15 and 16 was between 10 and 11 AM. DPH/matched placebo was administered on Day 16 between 3 and 4 PM. Simulated driving tests were conducted on Day 16 at around 5 PM. This time point was chosen as it corresponds to the approximate Tmax of gabapentin for subjects in the GEN group (7 hours after dosing) and the approximate Tmax of DPH for subjects in the active control group (2 hours after dosing). The simulated driving test consisted of a 5 minute practice drive, a 2 minute brake reaction time test and a 1 hour test drive along a simulated rural 2-lane highway. During the test drive subjects were asked to drive at a constant speed of 55 mph.

#### *Sponsor's Summary of Study XP083 results*

The primary outcome measure of this study was the change from Baseline in Standard Deviation of Lane Position (also called Lane Position Variability and abbreviated as LPV) at Day 16 (estimated Tmax). A mean increase from Baseline in LPV (0.15 ft) was detected in the GEN 1200 mg and GEN 1800 mg groups and a mean decrease (-0.10 ft) was observed in the placebo group. There was a treatment difference between the GEN 1200 mg group and placebo (0.25 ft, 95% CI [0.08, 0.42]) and between the GEN 1800 mg group and placebo (0.25 ft, 95% CI [0.09, 0.41]). The active control (DPH) also showed a mean increase from Baseline in LPV (0.16 ft) and an apparent treatment difference (0.26 ft, 95% CI [0.09, 0.42]) when compared with placebo. At the Day 16 assessment the adjusted mean changes in speed variability (SV) from Baseline for the placebo, GEN 1200 mg, GEN 1800 mg and DPH groups were -0.57, -0.11, 0.24 and -0.08 mph, respectively.

The proportion of subjects experiencing an increase from Baseline in simulated crashes changed from 21.4% to 28.6%, 9.1% to 18.2%, and 7.1% to 10.7% in the GEN 1200 mg, 1800 mg, and DPH groups, respectively, at the Day 16 (estimated Tmax driving assessment). The proportion of subjects who experienced crashes in the placebo group decreased from 9.1% at Baseline to 0 at Day 16.

Treatment with GEN 1200 mg, GEN 1800 mg, and DPH showed greater mean reduction from Baseline (Day -1) to Day 16 (estimated Tmax) than the placebo group in pre-drive and post-drive alertness VAS scores (pre-drive adjusted mean differences: -6.2, -15.4, and -18.3 mm, and post-drive adjusted mean differences: -16.8, -20.7, and -27.4 mm, respectively). The adjusted treatment difference in pre-drive and post-drive alertness VAS scores for all 3 active treatment groups, except the pre-drive score for the GEN 1200 mg group, were statistically different from the placebo group. There were no

treatment differences in the mean change from Baseline in the difference between pre and post drive VAS scores between the active treatment groups and placebo at Day 16.

For the Day 14 evening and Day 15 morning assessments the GEn 1800 mg group gave LPV results that were similar to the placebo group, whereas the GEn 1200 mg group had mixed results, with increased LPV on Day 14 (adjusted mean change from baseline for GEn 1200mg versus placebo: 0.17 ft versus -0.06 ft, 95% CI for the treatment difference [0.09, 0.37]), increased speed variability on Day 15 (adjusted mean change from baseline for GEn 1200mg versus placebo: 0.44 mph versus -0.29 mph, 95% CI for the treatment difference [0.13, 1.33]) and a higher number of simulated crashes on both days (GEn 1200mg versus placebo for Day 14: 6 [21.4%] versus 4 [12.1%], for Day 15: 10 (35.7%) versus 1 [3%]).

There was no evidence in this study of an effect of either dose of GEn when compared with placebo for **average** lane position, average speed or brake reaction time. Full results for simulated driving and other pharmacodynamic endpoints are presented in the clinical study report.

In summary, the results of this study demonstrated an effect of GEn on simulated driving performance at Tmax in some subjects dosed at 1200 mg and 1800 mg once daily, which was comparable with that observed at the Tmax of a single 50mg dose of DPH. GEn 1800 mg did not differ from placebo on driving assessments at Day 14 (evening after dosing) and Day 15 (the following morning; results for GEn 1200 mg were inconsistent at these time points).

## 2.2 Data Sources

At the time of review the simulated-driving safety study data was located as follows.

<\\Cdsub1\evsprod\NDA022399\0093\m5\datasets\rxp114111\analysis\datasets\stisim.xpt>

The sponsor's study report was found in the following directory location.

<\\Cdsub1\evsprod\NDA022399\0093\m5\53-clin-stud-rep\535-rep-effic-safety-stud\primary-rls\5354-other-stud-rep\rxp114111>

## 3 STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

The study under review, RXP114111, is a driving safety study done as a post-marketing requirement in normal subjects. Therefore, there is no evaluation of efficacy in this review.

## 3.2 Evaluation of Safety

Only driving safety, which study RXP114111 was primarily designed for investigating, is considered here. Please see the clinical review for a complete assessment of safety.

### 3.2.1 RXP114111

#### 3.2.1.1. Study Design and Analysis Plan

Study Initiation Date: 30-JUN-2011

Study Completion Date: 19-OCT-2011

The primary objective of the study was to assess the effect of gabapentin enacarbil (GEN) 600 mg once daily on simulated driving performance in healthy adult subjects.

This was a randomized, double-blind, double-dummy, active- and placebo-controlled, 3-period crossover study designed to assess the effect of GEN 600 mg on simulated driving performance in healthy adult subjects. Each subject participated in 3 dosing and simulated driving assessment periods.

Thirty-six healthy male and female adult subjects were enrolled in the study with the goal of having 30 subjects complete dosing and critical assessments. The total duration of the subject's participation in the study was up to approximately 9 weeks, which included up to a 28-day Screening Period, three 6-day Treatment Periods, 2 additional washout days, and an approximately 14-day Follow-up Period.

Subjects received each of the following 3 treatments in a randomized sequence: placebo, GEN 600 mg, and DPH 50 mg.

Simulated driving tests were conducted at Baseline before the start of dosing (on Day -1 in the evening between 7 and 9 PM, on Day 1 in the morning between 7 and 9 AM, and at midday between 11 AM and 1 PM), on Day 5 of each treatment period in the evening (7 to 9 PM), and on Day 6 of each treatment period in the morning (7 to 9 AM) and at midday (11 AM to 1 PM).

Gabapentin enacarbil has an extended-release profile, with time of occurrence of maximum plasma concentration ( $t_{max}$ ) occurring approximately 7 hours after dosing with food. With a dosing time of approximately 5 PM,  $t_{max}$  should generally occur late in the evening. For this present study, simulated driving assessments were conducted approximately 2 to 4 hours after dosing on Day 5 (7 to 9 PM) and on the following morning (7 to 9 AM, approximately 14 to 16 hours after dosing) and at midday (11 AM to 1 PM, approximately 18 to 20 hours after dosing) on Day 6 of each treatment period. These time points were selected because these represent times when subjects are likely to be driving (i.e., close to the times of morning and evening commuting periods) and were shown in a previous study (XP083) to demonstrate driving impairments in a similar range to those noted at the  $t_{max}$  endpoint.

## Simulated Driving Test

For the simulated driving test, each subject sat in a simulated automobile seat located within a sound- and light-attenuated room. Each subject completed a 5-minute practice drive to allow him or her to become familiar with the simulated environment and the handling characteristics of the simulated automobile. The practice drive consisted of a 2-lane highway environment with several gradual curves and oncoming vehicles that allowed for adaptation to the vehicle's handling and reduced potential learning effects.

After a 5-minute practice drive, each subject completed a 60-minute simulated driving test. The simulated driving test consisted of a 2-lane rural highway with gradual curves and oncoming vehicles approximately every 10 minutes. The subject was instructed to maintain a speed of 55 mph throughout the simulated driving test. Designated study center personnel were required to monitor all subjects throughout the simulated driving test by watching the computerized display of the roadway and driving simulator performance.

## Driving Simulation Variables

Measures such as lane position and speed will be continuously sampled at a rate of one time per second for the duration of the test. Each simulation will take around 61 minutes and the data from 1 minute to 61 minutes will be used for the one hour driving simulation analysis. Each 60-minute driving simulation is divided into six sequential 10-minute intervals ( $h=1$  to 6). These 10-minute intervals are referred to as epochs. The first epoch starts ( $h=1, i=1$  second) after the subject has driven the simulated vehicle 1000 feet following the start of the simulation.

- Lane Position Variability(LPV)

Lane position (LP) is measured as the difference in feet between the center of the simulated vehicle and the center line of the 26-foot wide paved roadway. When the simulated vehicle crosses over the center line into oncoming traffic this difference becomes negative. Lane position (ft) is measured once per second, and recorded electronically. Let  $LP_i$  be the lane position for the  $i$ th second ( $i=1$  to 3600). The average lane position, ALP is calculated as:

$$ALP = \sum_{i=1}^{3600} LP_i / 3600$$

Lane position variability (ft) for the 60-minute driving simulation is the standard deviation of  $LP_i$ . Let LPV be lane position variability for the entire 60-minute driving simulation test, then LPV will be computed as:

$$LPV = \left\{ \sum_{i=1}^{3600} (LP_i - ALP)^2 / 3599 \right\}^{\frac{1}{2}}$$

- Speed Variability

Speed variability is calculated in a similar fashion.

- Crash

A car crash is defined as a collision with an oncoming car, or when the distance to the center line was greater than 18 ft on either side of the road.

When crashes occur during the simulation, data collection is suspended while a crash sound effect plays (approximately 2 seconds), the vehicle's speed is set to 0 mph and its position is reset to 6 feet to the right of the roadway center line. Data collection resumes when control is

given back to the driver. Gaps in the data record when the driver does not have control of the car (i.e., following a crash) are not counted as part of the 60 minute simulation period.

Control of the car following a crash is returned to the driver, independent of whether the driver is awake and/or ready to resume driving. When a subject falls asleep and crashes, the simulator goes through the steps as outlined above, and control of the car is returned to the subject. At this point if the subject remains asleep, he/she will still have full control of the simulator and the run will continue. The administrator of the simulation is instructed not to wake up sleeping subjects. Subjects who continue to sleep will eventually crash, as the car has an automatic transmission. Unless the brake is pressed, the vehicle will creep forward and eventually drift off the road.

In the simulation, the number of crashes is set to 0 at the beginning. The value will be changed if there is a crash. The change value will be different depending on the type of crash that occurred. If the value changes by 1, which means the driver hit another vehicle, if it changes by 2 which means they went off the road and crashed. How many times the values changed indicates how many crashes occurred during the one hour driving test.

### **Alertness Visual Analogue Scale**

Each subject completed the alertness VAS by answering the question “How alert do you feel now?” by marking a point on a 100-mm horizontal line, where the left end of the scale was labeled “Extremely Sleepy” and the right end of the scale was labeled “Extremely Alert.” The alertness VAS was scored at pre- and post-simulated driving test such that higher scores indicated greater alertness; whereas, lower scores indicated reduced alertness.

### **Sample Size Considerations**

Approximately 36 subjects were planned for enrollment to ensure completion of 30 subjects (i.e., subjects completing all 3 treatment periods).

This study was designed to provide an estimate of the difference in mean LPV between active (GEN or DPH) and placebo groups. A sample size of 30 produces a 95% confidence interval (CI) equal to the sample mean plus or minus 0.153 when the estimated standard deviation (SD) is 0.41. This corresponds to the results observed in the XP083 study, where on Day 16 the placebo group had a mean (SD) LPV of 1.26 (0.31) feet and the DPH group had an LPV of 1.52 (0.50) feet, resulting in a 95% CI of (0.10, 0.43) for the treatment difference, i.e., a width of approximately 0.3 ft and an SD of the difference in means of 0.41.

Full details of the planned and performed analyses were provided in the Study RXP114111 Clinical Pharmacology Reporting and Analysis Plan (RAP), approved by the sponsor on 13-SEP-2011 (before database freeze).

### **Details of the Reporting and Analysis Plan**

The following analysis was to be performed for the change from baseline in lane position variability, speed variability, and the difference between pre-driving and post-driving alertness VAS scores: A mixed model repeated measures analysis of covariance was to be used for each driving simulation (Day 5 evening, Day 6 morning, and Day 6 midday)

using the PROC MIXED procedure in SAS. The model was to include period and treatment as fixed effects, subject as a random effect, and the appropriate baseline value as a covariate. No interaction terms were to be included in the primary model. No term representing carryover (i.e., sequence) was to be included in the primary model. Within subject measures (across period) were specified to have an unstructured covariance matrix and the Kenward-Roger approximation for the denominator degrees of freedom was to be used. Adjusted mean change from baseline estimates were to be derived for each treatment group using the OM<sup>1</sup> option within the LSMEANS statement. In addition, for each treatment group, the point estimate and its variability was to be presented as adjusted mean change from baseline and the standard error. For each pairwise treatment difference, a point estimate of each adjusted mean difference, the standard error of the difference, and a 95% confidence interval were to be presented.

If the assumptions underlying the mixed model repeated measures analysis described above were not met, a nonparametric version of analysis was to be used instead. This alternate analysis was to be performed based on the modified ridit score of the change value (lane position variability, speed variability, and the difference between pre-driving and post-driving alertness VAS scores). Change value was to be ranked and the ridit score within each period was to be obtained. Repeated measures ANCOVA model with fixed effects for period and treatment, random effect for subject, and modified ridit score of the appropriate baseline was to be fitted. An unstructured covariance matrix was specified for within subject measures and Kenward-Roger approximation for the denominator degrees of freedom was to be used.

No carryover effects were expected in this study due to the duration of the treatment periods (it was expected that each driving simulation test was sufficiently delayed that the effects of previous treatments would have been eliminated). However, it was thought that a period effect may be observed. To assess this for LPV, a separate supportive analysis was to be performed to enable the assessment of homogeneity of the treatment differences across periods: the model used in the primary analysis was to be expanded to additionally include a term for the treatment\*period interaction which was to be assessed relative to a two-sided 15% alpha level. However, the primary inference was to be based on the model excluding the treatment\*period interaction.

To explore the impact of extreme changes in LPV, “extreme” values were identified before unblinding as those falling in the top 15% of values based on the range of change in LPV (using all blinded postbaseline data, regardless of treatment groups and time points). Groupings of change in LPV were determined based on the percentiles of the range of change in LPV, as described in the RAP. The number and percentage of subjects that fell within each LPV grouping were summarized within treatment group for each driving simulation time point.

Subjects were summarized by the number of simulated crashes at each driving simulation time point by treatment group. In addition, characteristics (i.e., age, sex, race, whether or not an ongoing AE was present, alertness VAS, and plasma gabapentin concentration

---

<sup>1</sup> OM stands for Observed Margins; it is reasonable when one wants inferences to apply to a population that is not necessarily balanced (e.g., subjects with some but not all periods) but has the margins (e.g., periods with at least one record) observed in the dataset.

levels) of subjects for drives with any simulated crashes were listed by subject and treatment.

### **Analysis Populations**

The All Subjects Population was defined as all subjects who were enrolled in the study.

The Pharmacokinetics (PK) Population was defined as all subjects who received at least 1 dose of GEN and had at least 1 concentration reported.

The Safety Population was defined as all subjects who were randomly assigned to treatment and received at least 1 dose (or any portion of a dose) of any treatment.

The Intent-to-Treat (ITT) Population was defined as all subjects in the Safety Population who completed at least 1 baseline and 1 postbaseline simulated driving assessment.

Changes in the analyses planned in the RAP and those reported in the sponsor's study report are described next.

#### **Modified Statistical Analysis Plan which was the Basis for Sponsor's Study Report**

The primary analysis population for the study was the ITT Population, and all driving simulation and alertness VAS assessment analyses were conducted on this population. Change from Baseline in LPV, SV, pre-driving alertness VAS scores, post-driving alertness VAS scores, and the difference between pre-driving and post-driving alertness VAS scores (pre-driving VAS score – post-driving VAS score) for each driving simulation time point were summarized by treatment, regardless of period or treatment sequence.

The following analysis was performed for the change from Baseline in LPV, SV, and the difference between pre-driving and post-driving alertness VAS scores: A mixed-model repeated-measures analysis of covariance was used for each driving simulation (Day 5 evening, Day 6 morning, and Day 6 midday) using the PROC MIXED procedure of SAS software. This model included period and treatment as fixed effects, subject as a random effect, and the appropriate baseline value as a covariate. No interaction terms were included in the primary model. No term representing carryover (i.e., sequence) was included in the primary model. Within-subject measures (across period) were specified to have a variance components covariance structure and the Kenward-Roger approximation for the denominator degrees of freedom was used. Adjusted mean changes from Baseline estimates were derived for each treatment group using the OM option within the LSMEANS statement.

### **Changes in Conduct of the Study or Planned Analyses**

There was one change in the conduct of the study. To ensure an adequate washout of DPH before administration of study drug in the next dosing period, placebo was administered on Day 6 of Treatment Periods 1 and 2, as stated in the protocol. However, the study center erroneously included an additional drug-free day between Treatment Periods 1 and 2 and also between Treatment Periods 2 and 3 for all subjects. Subjects did not have any study procedures performed on the extra washout day. The extra washout day did not pose an additional safety risk to the subjects and was not considered by the sponsor to have affected the outcome of the study. No protocol amendment was generated for this change.

There was one change to the planned analyses. The change was made after unblinding and the RAP was not amended. A variance components covariance structure for the within-subjects measure was used instead of an unstructured variance matrix. According to the sponsor for crossover designs, an unstructured covariance matrix is not appropriate for use in the model [Littell, 2006]. The following excerpt from the sponsor's study report provides additional reasoning for the change. "Specifying type=UN (unstructured variance matrix) as an option in the random statement estimates different variances for different subjects and different covariances for each subject pair. Since subjects are independent from one another, an unstructured variance matrix is not appropriate. In this study, the subject is treated as a random effect. Therefore, the variance components covariance structure (type=VC) was a more appropriate option."

*Reviewer's Comments:*

*To this reviewer it seems there is some merit to the sponsor's post-hoc claim that the unstructured covariance that they prespecified for the primary analysis model is not appropriate for crossover studies, at least not if it is assumed the same for all treatment sequences. For example, assuming the "unstructured" covariance, for the two sequences ABC and CAB the first sequence would have the same correlation between measurements under B and C as the second sequence had under A and B because the corresponding periods are the same. However, they would in general have different correlations between A and B between the two sequences since A and B occur in different periods in the two sequences and for an unstructured covariance matrix the correlation depends on the particular periods in which treatments A and B occur. Also, in general, the variance under treatment A would differ between the two sequences because treatment A occurs in different periods and the "unstructured" covariance matrix allows for different variances between periods. Similarly, the variances under treatment B (and C) would also differ in general between these two sequences since the periods that the particular treatment is given in differ between the sequences.*

*The problematic assumption associated with the "unstructured" covariance prescription seems to be that all sequences have the same correlation and variance pattern which forces variances under the same treatment to differ between sequences and variances under different treatments to be the same when the period that the two different treatments are administered in is the same (of course in this case the sequences are necessarily different). Nevertheless, this reviewer found that the post-hoc change to a simple random effect for subject within sequence did not seem to alter the significance of any of the group differences compared to the original specification for the covariance structure. The latter covariance specification is also an established method in the analysis of crossover studies.*

*Note also that the sponsor's nonparametric sensitivity analysis ranks LPV within each period and then fits a mixed model for repeated measures of the ranks with fixed effects for treatment and period. However, it seems that a period effect shouldn't exist except possibly if there is a carryover effect since in the absence of missing data the sum of the ranks from any period is the same by design.*

### 3.2.1.2. Subject Disposition and Demographic Characteristics

Table 2 summarizes subject disposition and demographics. Of the 36 subjects enrolled, 35 subjects (97%) completed the study and 1 subject was withdrawn prematurely owing to an Adverse Event (AE).

**Table 2 RXP114111 : Subject Disposition and Demographic Characteristics**

	<b>Overall N=36</b>
<b>Number of Subjects</b>	
Number of subjects completed, n (%)	35 (97)
Number of subjects discontinued, n (%)	1 (3)
Reasons for discontinuation, n (%)	
Adverse event	1 (3)
Number of subjects in PK Population, n (%)	35 (97)
Number of subjects in ITT Population, n (%)	36 (100)
Number of subjects in Safety Population, n (%)	36 (100)
<b>Demographics</b>	
<b>Age (years), Mean (SD)</b>	36.6 (11.75)
<b>Sex, n (%)</b>	
Female	16 (44)
Male	20 (56)
<b>Height (cm), Mean (SD)</b>	167.36 (7.375)
<b>Weight (kg), Mean (SD)</b>	72.20 (11.438)
<b>Body Mass Index (kg/m<sup>2</sup>), Mean (SD)</b>	25.67 (2.874)
<b>Ethnicity, n (%)</b>	
Hispanic or Latino	21 (58)
Not Hispanic or Latino	15 (42)
<b>Race, n (%)</b>	
African American/African Heritage	9 (25)
Asian - Japanese Heritage	1 (3)
White - White/Caucasian/European Heritage	25 (69)
White and African American/African Heritage	1 (3)

Note: This table was copied from page 24 of the sponsor's study report

### 3.2.1.3. Sponsor's Results

Mean (SD) LPV at Baseline was 1.24 ft (0.271), 1.30 ft (0.279), and 1.24 ft (0.259) for the Day - 1 evening, Day 1 morning, and Day 1 midday time points, respectively (Table 3). Generally similar results in adjusted mean change from Baseline in LPV (ft) were observed for GEN and placebo at all of the time points tested (Day 5 evening: GEN -0.01 [SE 0.041], placebo -0.01 [SE 0.041]; Day 6 morning: GEN 0.01 [SE 0.040], placebo 0.04 [SE 0.040]; and Day 6 midday: GEN 0.03 [SE 0.031], placebo 0.06 [SE 0.031]). After a single dose of DPH, there was a mean increase from Baseline in LPV compared with placebo at the Day 5 evening time point (0.17 ft; 95% CI: 0.08, 0.25) when treatment differences were analyzed. Generally similar results in mean change from Baseline in LPV were observed for DPH and placebo at the Day 6 morning (-0.01 ft; 95% CI: -0.08, 0.07) and Day 6 midday (0.00 ft; 95% CI: -0.05, 0.05) time points. Assay sensitivity was shown by the driving impairment observed with DPH treatment at the Day 5 evening time point and lack of impairment with DPH treatment on the following day (Day 6) at both the morning and midday time points.

Mixed-model repeated-measures analysis of covariance performed for change from Baseline in LPV generated the aforementioned adjusted means and differences in means from Baseline. The results confirmed the significant treatment effect at the Day 5 evening time point for DPH. There was an apparent treatment by period interaction that upon further exploration was determined to be quantitative rather than qualitative, therefore not impacting the conclusions of the analysis. Mixed-model repeated measures analysis of covariance results on change from Baseline in LPV are summarized in Table 3.

***Reviewer's Comment: The sponsor states that there was a treatment by period interaction ( $p=0.082$ ) that upon further exploration was quantitative rather than qualitative. In particular, this reviewer found that the estimate of the DPH vs. placebo difference in the second period at the Day 5 Evening timepoint was numerically but not significantly different favoring placebo ( $-0.03 \pm 0.08$  S.E.,  $p=0.72$ ), whereas in the other two periods the difference was nominally significant favoring DPH ( $0.22 \pm 0.08$  S.E. and  $0.32 \pm 0.08$  S.E.). The average of the three period specific differences ( $.17 \pm 0.08$  S.E.), DPH vs. placebo, was also nominally significant favoring DPH over placebo. Since the average of the period specific treatment differences was nominally significant this may not be a big issue and so it seems that assay sensitivity in LPV at the Day 5 Evening timepoint is reasonably well established in this trial. The sponsor also argued that this interaction was not important because it was driven by 1 patient who had multiple crashes and the largest change in LPV.***

***The sponsor also noted a treatment by period interaction with a p-value of 0.11 for the Day 6 Morning timepoint. This reviewer found that this seems to have been mostly influenced by the DPH vs. Placebo group comparison rather than by the GEN vs. Placebo group comparison (in 2 of the 3 periods as well as averaged across periods GEN was estimated as numerically better***

*in LPV). Based on this and given the relatively high p-value it is not considered a significant issue by this reviewer.*

Table 3 RXP114111: Change in Lane Position Variability

Time Point/ Statistic for LPV (ft)	Baseline N=36	Placebo Treatment Period N=36	GEN 600 mg Treatment Period N=35 <sup>a</sup>	DPH 50 mg Treatment Period N=36 <sup>b</sup>
<b>Day 5 PM</b>				
Mean LPV (SD)	1.24 (0.271)	1.24 (0.276)	1.24 (0.320)	1.40 (0.380)
Change from Baseline:				
Adjusted Mean (SE)		-0.01 (0.041)	-0.01 (0.041)	0.16 (0.041)
Trt Diff vs PBO (95% CI)			-0.01 (-0.09, 0.08)	<b>0.17 (0.08, 0.25)</b>
Trt Diff vs DPH (95% CI)			<b>-0.17 (-0.26, -0.09)</b>	
<b>Day 6 AM</b>				
Mean LPV (SD)	1.30 (0.279)	1.34 (0.303)	1.31 (0.324)	1.33 (0.309)
Change from Baseline:				
Adjusted Mean (SE)		0.04 (0.040)	0.01 (0.040)	0.03 (0.040)
Trt Diff vs PBO (95% CI)			-0.03 (-0.11, 0.04)	-0.01 (-0.08, 0.07)
Trt Diff vs DPH (95% CI)			-0.03 (-0.10, 0.04)	
<b>Day 6 Midday</b>				
Mean LPV (SD)	1.24 (0.259)	1.30 (0.300)	1.28 (0.335)	1.30 (0.318)
Change from Baseline:				
Adjusted Mean (SE)		0.06 (0.031)	0.03 (0.031)	0.06 (0.031)
Trt Diff vs PBO (95% CI)			-0.02 (-0.08, 0.03)	0.00 (-0.05, 0.05)
Trt Diff vs DPH (95% CI)			-0.02 (-0.08, 0.03)	

Note: this Table was copied from page 38 of the sponsor's study report

### Extreme Values

To further assess a potential treatment effect, an evaluation of subjects with relatively large LPV values was performed to determine the impact of these individual values.

Extreme values were predefined as those greater than the 85<sup>th</sup> percentile (i.e., those values occurring in the top 15% of all values (across treatment periods and postbaseline time points). The 85<sup>th</sup> percentile was approximately 0.26 ft. The 95<sup>th</sup> percentile was approximately 0.48 ft.

As shown in Table 4, most of the simulated drives had very little change in LPV. A majority of the simulated drives in any treatment period and at any time point had either a decrease in LPV or a mean increase of less than 0.18 ft. The LPV values noted to be above the 85<sup>th</sup> percentile (>0.26 ft) were similarly distributed across the time points, occurring in 18 of the Day 5 evening simulated drives, 17 of the Day 6 morning simulated drives, and 12 of the Day 6 midday simulated drives.

More than twice as many DPH-treated subjects experienced these larger increases in LPV compared with the other 2 treatments at the Day 5 evening point. Of these increases in LPV >0.26 ft, 7 (0 in the placebo treatment period, 1 in the GEn treatment period, and 6 in the DPH treatment period) were >0.48 ft (ranging from 0.4833 to 0.9003 ft), with DPH-treated subjects exhibiting a greater impairment in simulated driving ability as measured by LPV compared with subjects treated with placebo or GEn.

**Table 4 RXP114111: Large Changes in Lane Position Variability (ITT Population)**

Time Point/ LPV Percentile	Placebo Treatment Period N=36 n (%)	GEN 600 mg Treatment Period N=35 n (%)	DPH 50 mg Treatment Period N=36 <sup>a</sup> n (%)
<b>Day 5 PM</b>			
0 <sup>th</sup> -85 <sup>th</sup>	31 (86)	33 (94)	24 (69)
85 <sup>th</sup> -95 <sup>th</sup>	5 (14)	1 (3)	5 (14)
95 <sup>th</sup> -100 <sup>th</sup>	0	1 (3)	6 (17)
<b>Day 6 AM</b>			
0 <sup>th</sup> -85 <sup>th</sup>	28 (78)	31 (89)	31 (86)
85 <sup>th</sup> -95 <sup>th</sup>	6 (17)	2 (6)	3 (8)
95 <sup>th</sup> -100 <sup>th</sup>	2 (6)	2 (6)	2 (6)
<b>Day 6 Midday</b>			
0 <sup>th</sup> -85 <sup>th</sup>	32 (89)	31 (89)	32 (89)
85 <sup>th</sup> -95 <sup>th</sup>	4 (11)	2 (6)	4 (11)
95 <sup>th</sup> -100 <sup>th</sup>	0	2 (6)	0

Data Source: [Table 12.3](#)

a. N=35 at Day 5 evening time point.

Note: The 85<sup>th</sup> percentile was approximately 0.26 ft. The 95<sup>th</sup> percentile was approximately 0.48 ft.

DPH=diphenhydramine, GEN=gabapentin enacarbil, LPV=lane position variability

Note: This table was copied from page 40 of the sponsor's study report

**Speed Variability (SV):**

Mean (SD) SV at Baseline was 1.26 mph (0.905), 1.31 mph (0.739), and 1.16 mph (0.573) for the Day -1 evening, Day 1 morning, and Day 1 midday time points, respectively (Table 5).

Generally similar results in adjusted mean change from Baseline in SV (mph) were observed for GEn and placebo at all of the time points tested (Day 5 evening: GEn 0.21 [SE 0.228], placebo 0.04 [SE 0.227]; Day 6 morning: GEn 0.21 [SE 0.126], placebo 0.21 [SE 0.125]; and Day 6 midday: GEn 0.42 [SE 0.170], placebo 0.27 [SE 0.169]). After a single dose of DPH, there was a mean increase from Baseline in SV compared with placebo at the Day 5 evening time point (0.56 mph; 95% CI: 0.24, 0.89) when treatment differences were analyzed. Generally similar results in mean change from Baseline in SV were observed for DPH and placebo at the Day 6 morning (-0.09 mph; 95% CI: -0.37, 0.20) and Day 6 midday (0.22 mph; 95% CI: -0.06, 0.49) time points. Assay sensitivity was shown by the driving impairment observed with DPH treatment at the Day 5 evening time point and lack of impairment with DPH treatment on the following day (Day 6) at both the morning and midday time points.

**Table 5 RXP114111: Change in Speed Variability (mph) (ITT Population)**

Time Point/ Statistic for SV (mph)	Baseline N=36	Placebo Treatment Period N=36	GEN 600 mg Treatment Period N=35 <sup>a</sup>	DPH 50 mg Treatment Period N=36 <sup>b</sup>
<b>Day 5 PM</b>				
Mean SV (SD)	1.26 (0.905)	1.29 (0.788)	1.46 (1.501)	1.81 (1.791)
Change from Baseline:				
Adjusted Mean (SE)		0.04 (0.227)	0.21 (0.228)	0.60 (0.228)
Trt Diff vs PBO (95% CI)			0.17 (-0.16, 0.49)	<b>0.56 (0.24, 0.89)</b>
Trt Diff vs DPH (95% CI)			<b>-0.40 (-0.72,-0.07)</b>	
<b>Day 6 AM</b>				
Mean SV (SD)	1.31 (0.739)	1.52 (1.000)	1.53 (1.001)	1.44 (0.769)
Change from Baseline:				
Adjusted Mean (SE)		0.21 (0.125)	0.21 (0.126)	0.12 (0.125)
Trt Diff vs PBO (95% CI)			0.00 (-0.29, 0.29)	-0.09 (-0.37, 0.20)
Trt Diff vs DPH (95% CI)			0.09 (-0.20, 0.37)	
<b>Day 6 Midday</b>				
Mean SV (SD)	1.16 (0.573)	1.44 (0.958)	1.59 (1.161)	1.65 (1.374)
Change from Baseline:				
Adjusted Mean (SE)		0.27 (0.169)	0.42 (0.170)	0.49 (0.169)
Trt Diff vs PBO (95% CI)			0.14 (-0.13, 0.42)	0.22 (-0.06, 0.49)
Trt Diff vs DPH (95% CI)			-0.07 (-0.35, 0.20)	

Data Source: [Table 12.4](#) and [Table 12.5](#)

a. N=36 at Baseline.

b. N=35 at Day 5 evening time point.

Note: Bolded cells identify 95% CIs for treatment differences that do not include 0, indicating an apparent difference between the 2 treatments. The analysis method was mixed-model repeated measures with treatment and period as fixed categorical effects, baseline SV as fixed continuous effect, and subject as a random effect.

CI=confidence interval, Diff=difference, DPH=diphenhydramine, GEN=gabapentin enacarbil, PBO=placebo, SV=speed variability, Trt=treatment, vs=versus

Note: This table copied from page 42 of sponsor's study report

### Number of Simulated Driving Crashes:

At the Day 5 evening time point, no subject experienced a simulated driving crash at the corresponding Baseline assessment (Day -1 evening) or during placebo or GEN treatment. During DPH treatment, 2 subjects (6%) experienced 1 simulated driving crash and 1 subject (3%; Subject (b) (6)) experienced 2 simulated driving crashes (Table 6).

At the Day 6 morning time point, 2 subjects (6%) experienced a simulated driving crash at the corresponding Baseline assessment (Day 1 morning), 1 subject (3%) experienced a simulated driving crash during placebo treatment, and 1 subject (3%) experienced a simulated driving crash during GEN treatment. No subject experienced a simulated driving crash during DPH treatment.

At the Day 6 midday time point, 1 subject (3%) experienced a simulated driving crash at the corresponding Baseline assessment (Day 1 midday) and 3 subjects (8%) experienced 1 simulated driving crash during DPH treatment. During GEN treatment, 2 subjects (6%) experienced 1 simulated driving crash and 1 subject (3%; Subject <sup>(b) (6)</sup>) experienced 2 simulated driving crashes. No subject experienced a simulated driving crash during placebo treatment.

**Table 6 RXP114111 Number and Percentage of Subjects with Simulated Driving Crashes (ITT Population)**

Time Point/ Number of Simulated Driving Crashes	Baseline N=36 n (%)	Placebo Treatment Period N=36 n (%)	GEN 600 mg Treatment Period N=35 <sup>a</sup> n (%)	DPH 50 mg Treatment Period N=36 <sup>b</sup> n (%)
<b>Day 5 PM</b>				
0	36 (100)	36 (100)	35 (100)	32 (91)
1	0	0	0	2 (6)
2	0	0	0	1 (3)
<b>Day 6 AM</b>				
0	34 (94)	35 (97)	34 (97)	36 (100)
1	2 (6)	1 (3)	1 (3)	0
2	0	0	0	0
<b>Day 6 Midday</b>				
0	35 (97)	36 (100)	32 (91)	33 (92)
1	1 (3)	0	2 (6)	3 (8)
2	0	0	1 (3)	0

Data Source: [Table 12.6](#)

a. N=36 at Baseline.

b. N=35 at Day 5 evening time point.

DPH=diphenhydramine, GEN=gabapentin enacarbil

Note: This table was copied from page 44 of sponsor's study report

**Reviewer's Comment: The Day 6 Midday results suggest a possible increase in crashing due to GEN 600 mg although based on McNemar's test the difference compared to placebo is not**

*statistically significant, one sided p=0.125. Note that only descriptive statistics were prespecified for crashes data but McNemar's test is appropriate for analysis of matched pairs (in this case observations of crashes in different periods under GEN and Placebo for the same subject) and may be more appropriate here because of the low number of observed crashes than a typical analysis requiring a large sample assumption or a large expected number of crashes.*

**Crashes in Pilot Study XP088**

The following table shows the crashes in the pilot study XP088 which compared 15 normal subjects to 15 RLS subjects without any study treatment. This suggests that the following morning when any driving impairment would be expected RLS patients had numerically more crashes. The study was really too small to be conclusive though.

**Table 7 Study XP088 Number of Crashes by Study Group**

	Normal N=15	RLS N=15	Total N=30
<b>Day 1, 4PM – Overall (0 to 60 min), n (%)</b>			
0 Crashes	13 (86.7)	15 (100.0)	28 (93.3)
1 Crash	2 (13.3)	0 (0.0)	2 (6.7)
2 Crashes	0 (0.0)	0 (0.0)	0 (0.0)
3 Crashes	0 (0.0)	0 (0.0)	0 (0.0)
<b>Day 2, 8AM – Overall (0 to 60 min), n (%)</b>			
0 Crashes	15 (100.0)	13 (86.7)	28 (93.3)
1 Crash	0 (0.0)	1 (6.7)	1 (3.3)
2 Crashes	0 (0.0)	0 (0.0)	0 (0.0)
3 Crashes	0 (0.0)	1 (6.7)	1 (3.3)

Data Source: [Table 7.7](#).

Note: Number of crashes over the indicated time interval, where the simulated vehicle went off the 26-foot wide roadway by more than 5 feet or hit an oncoming vehicle.

Note: This table was copied from page 39 of the sponsor's XP088 study report

**Overall Summary of Crashes Data**

In summary there is a suggestion from study RXP114111 that there may be more crashes on GEN 600 mg than placebo in normal subjects and from study XP088 that there may be more crashes expected in untreated RLS patients than in untreated normal subjects.

These observations were not statistically significant but these studies were small and may not have had adequate power to detect an effect on crashes (DPH showed numerically more crashes than placebo on Day 5 Evening, similar to that seen for Gen 600 mg on Day 6 Midday, but this crash difference was also not statistically significant).

## **Alertness Visual Analogue Scale**

The alertness VAS was scored such that higher scores indicate greater alertness; whereas, lower scores indicate reduced alertness. Therefore, an increase in VAS score from pre- to post-simulated driving test represents an increase in alertness and a decrease from pre- to post-simulated driving test represents a decrease in alertness.

The Baseline mean alertness VAS scores ranged from 66.8 to 69.2 mm at pre-simulated driving test and 57.1 to 68.6 mm at post-simulated driving test, with changes in alertness ranging from -0.1 to 9.8 mm.

Across all treatment groups, the changes in alertness (pre- versus post-simulated driving test) were either decreases or minimal changes (Day 5 evening: decreases ranging from 4.9 to 19.0 mm, Day 6 morning: decreases ranging from 8.8 to 11.4 mm, Day 6 midday: minimal changes ranging from -1.2 to 3.5 mm). The largest decrease in alertness was observed at the Day 5 evening time point in the DPH treatment period; the treatment differences were 12.9 mm (95% CI: 4.50, 21.32) for DPH versus placebo and -14.3 mm (95% CI: -22.78, -5.82) for GEN versus DPH. No notable difference was observed at the Day 5 evening time point between GEN and placebo (-1.4 mm, 95% CI: -9.80, 7.02). No notable differences in pre- versus post-simulated driving test VAS scores were observed among treatment periods at either the Day 6 morning or the Day 6 midday time points (Table 8).

**Table 8 RXP114111: Alertness Visual Analogue Scale**

Time Point/ Statistic for VAS (mm)	Baseline N=36	Placebo Treatment Period N=36	GEN 600 mg Treatment Period N=35 <sup>a</sup>	DPH 50 mg Treatment Period N=36 <sup>b</sup>
<b>Day 5 PM</b>				
Mean VAS (SD) Change (Pre-Test – Post-Test)	8.7 (17.16)	6.3 (16.18)	4.9 (18.77)	19.0 (23.08)
Change from Baseline:				
Adjusted Mean (SE)		-2.3 (3.22)	-3.7 (3.26)	10.6 (3.26)
Trt Diff vs PBO (95% CI)			-1.4 (-9.80, 7.02)	<b>12.9 (4.50, 21.32)</b>
Trt Diff vs DPH (95% CI)			<b>-14.3 (-22.78, -5.82)</b>	
<b>Day 6 AM</b>				
Mean VAS (SD) Change (Pre-Test – Post-Test)	9.8 (15.98)	11.4 (17.43)	8.8 (25.00)	10.1 (21.26)
Change from Baseline:				
Adjusted Mean (SE)		1.6 (3.57)	-1.3 (3.60)	0.3 (3.57)
Trt Diff vs PBO (95% CI)			-2.9 (-9.93, 4.16)	-1.3 (-8.25, 5.70)
Trt Diff vs DPH (95% CI)			-1.6 (-8.65, 5.44)	
<b>Day 6 Midday</b>				
Mean VAS (SD) Change (Pre-Test – Post-Test)	-0.1 (18.37)	-1.2 (20.84)	3.5 (20.67)	0.3 (17.72)
Change from Baseline:				
Adjusted Mean (SE)		-1.1 (3.27)	3.5 (3.32)	0.4 (3.27)
Trt Diff vs PBO (95% CI)			4.7 (-4.15, 13.45)	1.5 (-7.23, 10.23)
Trt Diff vs DPH (95% CI)			3.2 (-5.65, 11.95)	

Data Source: [Table 12.8](#) and [Table 12.9](#)

a. N=36 at Baseline.

b. N=35 at Day 5 evening time point.

Note: Bolded cells identify 95% CIs for treatment differences that do not include 0, indicating an apparent difference between the 2 treatments. The analysis method was mixed-model repeated measures with treatment and period as fixed categorical effects, baseline alertness VAS as fixed continuous effect, and subject as a random effect.

CI=confidence interval, Diff=difference, DPH=diphenhydramine, GEN=gabapentin enacarbil, PBO=placebo,

Trt=treatment, VAS=visual analogue scale, vs=versus

Note: This table was copied from page 46 of the sponsor’s study report

### **Sponsor's Conclusions from Simulated Driving Studies**

While driving impairment was demonstrated in Study XP083 (the original driving simulation study that was included in the original NDA), this parallel group study was performed in subjects with RLS at a higher than recommended dose (600 mg/day for the treatment of moderate-to-severe primary RLS) of GEN (1200 and 1800 mg once daily). A second driving simulation study (RXP114111) was performed post approval to determine if driving performance would be impacted at the recommended dose of 600 mg once daily. This study utilized a cross-over design to account for baseline variability in driving performance among subjects. The result of this study demonstrated that the effect on simulated driving performance for healthy volunteers receiving a dose of 600 mg of HORIZANT for 5 days was similar to that for subjects receiving placebo, demonstrating a lack of effect on simulated driving performance. This lack of effect persisted for all three assessment time points within 20 hours post-dose. DPH 50 mg impaired simulated driving ability at the Day 5 evening time point only, demonstrating assay sensitivity. Although Study RXP114111 did not evaluate timepoints beyond Day 5/6, the lack of an effect at a 600 mg once daily dose of GEN suggests to the sponsor that the potential for an effect at later time points is not expected, and therefore in the sponsor's opinion a second study evaluating persistence beyond Day 5/6 is not warranted.

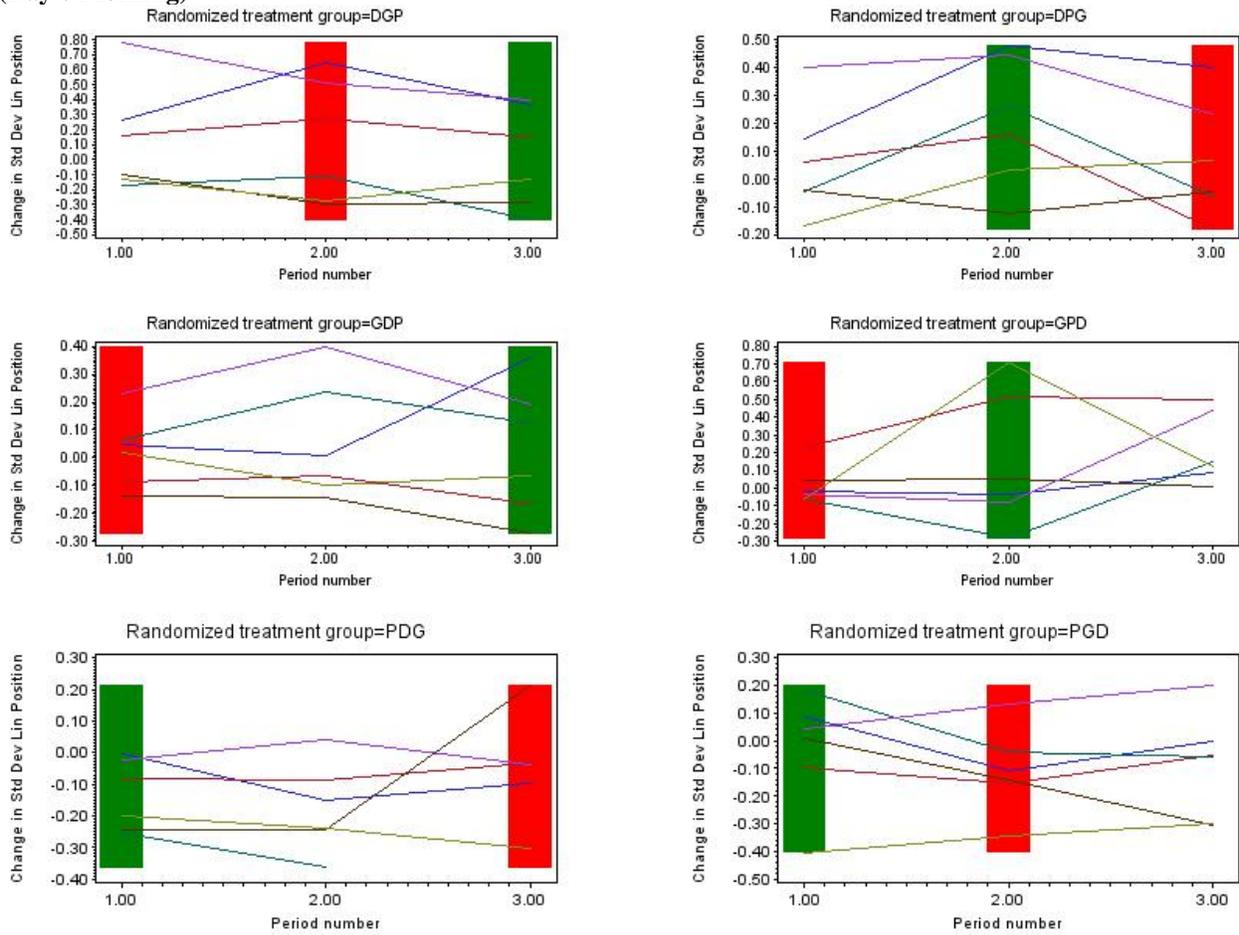
#### **3.2.1.4. Reviewer's Results**

This reviewer verified the sponsor's primary analyses for study RXP114111.

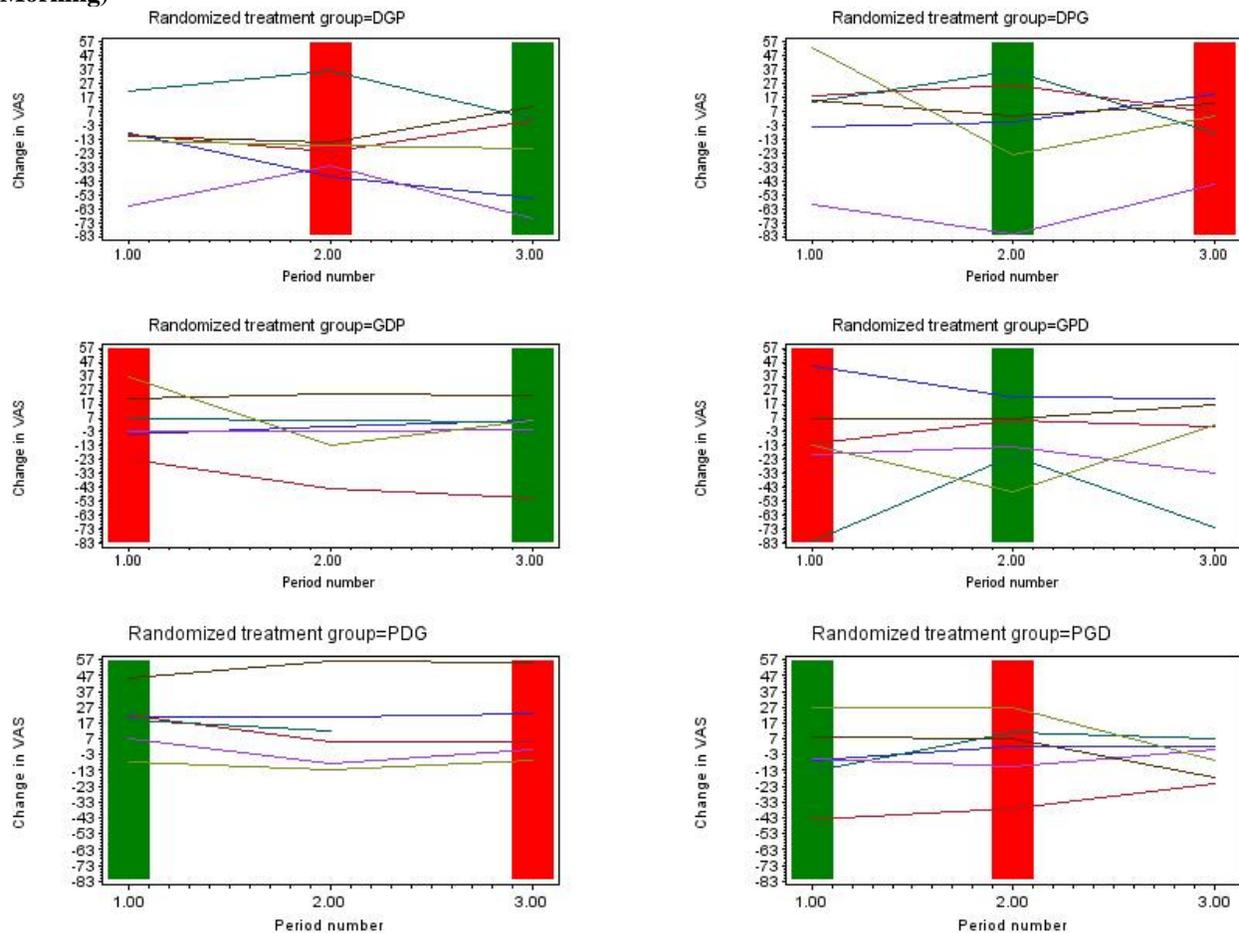
The following figure displays subject profiles of standard deviation of linear position (LPV) by assigned treatment sequence across the three periods. The red bar is to highlight the GEN period and the green bar is to highlight the placebo period for ease of comparison of these two periods which vary across assigned sequence. The one dropout was in the PDG sequence and completed all but the GEN period. Imputing the worst observed LPV for the last period for this patient did not alter the significance of the GEN versus placebo comparison for Day 5 Evening, Day 6 Morning, or Day 6 Midday.

If this dropout patient had a crash imputed in the last period, the missing GEN period, the one-sided p-value for McNemar's test for a difference between GEN and placebo in crashes would be 0.0625 instead of the value of 0.125 with this patient missing. Note that the sponsor only planned descriptive statistics for crashes data but McNemar's test is appropriate for matched pairs (number of crashes in each of GEN and Placebo periods for the same subject) and data with small numbers of crashes.

**Figure 1 Subject Profiles of Standard Deviation of Linear Position (LPV) by Assigned Treatment Sequence (Day 6 Morning)**



**Figure 2 Subject Profiles of Change in VAS Post-Test from Baseline by Assigned Treatment Sequence (Day 6 Morning)**



#### 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

##### 4.1 Gender, Race, Age, and Geographic Region

The mean age in RXP114111 was 36.6 with a range from 19 to 57. The proportion of females was 16/36 or 44%. The proportion of Whites was 25/36 or 69% and the proportion classified as having an ethnicity of Hispanic was 21/36 or 58% (42% were classified as non-Hispanic). It is difficult to say anything conclusive about potentially differential effects by age, gender, or ethnicity because this is a small crossover study and the treatment sequences are not completely balanced within these subgroups (which could confound any subgroup effects).

Mean age was 46.8 (11.62 S.D.) with a range of 21 to 70 in the earlier parallel group study XP083 in RLS. Mean age in RXP114111 was 36.6 (11.75 S.D.). Average weight in XP083 was 78.8(15.36 S.D.) as compared to 72.2 (11.438 S.D.) in RXP114111. Mean Height was 169.9 (10.08 S.D.) in XP083 vs. 167.36 (7.375 S.D.) in RXP114111. In XP083 89.1% were not Hispanic or Latino as compared to 42% in RXP114111. In XP083 race was 99%

Caucasian, but in RXP114111 69% were Caucasian, 25% were African American, and 6% were designated as 'Other'. Because of these demographic population differences between studies XP083 and RXP114111 it seems questionable to extrapolate or try to bridge the specific GEn dose result for the healthy population of RXP114111 to the general restless leg syndrome population (or that of study XP083). However, the sponsor seems to be doing this and it seems to this reviewer that without making such an extrapolation or bridging the question remains whether the GEn 600 mg dose affects driving safety in the drug's targeted population under consideration here, i.e., restless leg syndrome.

The RXP114111 study was conducted at a single center in the United States. Therefore, there is no geographic region information provided by this study.

#### **4.2 Other Special/Subgroup Populations**

No other subgroups were analyzed by this reviewer.

### **5 SUMMARY AND CONCLUSIONS**

#### **5.1 Statistical Issues and Collective Evidence**

There were the following notable differences in study populations between study XP083 and RXP114111 which makes bridging the healthy subject results of RXP114111 back to the RLS population (which the sponsor seems to be trying to do) perhaps even more questionable than it would ordinarily be between two more similar studies.

- XP083 was an RLS population whereas RXP114111 was a normal population
- In XP083 Mean Age was 46.8 (11.62 S.D.) with a range of 21 to 70, whereas Mean Age in RXP114111 was 36.6 (11.75 S.D.)
- In XP083 Mean Weight was 78.8(15.36 S.D.) as compared to 72.2 (11.438 S.D.) in RXP114111.
- In XP083 Mean Height was 169.9 (10.08 S.D.) as compared to 167.36 (7.375 S.D.) in RXP.
- In XP083 89.1% were not Hispanic or Latino as compared to 42% in RXP114111.
- In XP083 race was 99% Caucasian but in RXP114111 69% were Caucasian, 25% were African American, and 6% were Other.

This RXP114111 study was performed in a healthy population rather than in the population for which the drug is indicated, restless leg syndrome. An earlier study (XP088) which compared driving without any drug intervention in either the healthy population or the targeted population

(restless leg syndrome) found no significant differences between these groups. However, the study was very small with a total size of 30 patients, 15 per group, so it is possible that important differences exist between the healthy population and the target population but that they were missed due to a lack of power in that study. There was also a significant age difference between the healthy population and the disease population in that study (35.9 +/- 9.13 S.D. healthy vs. 52.6 +/- 12.6 S.D. restless leg syndrome) which may affect driving habits. The sponsor seems to be relying on this small pilot study to justify bridging from the normal subjects as in study RXP114111 to RLS subjects as in study XP083. This seems questionable because they did not demonstrate equivalence in study XP088 they only failed to detect significant differences, but with 15 patients per group there was probably low power to do so.

This reviewer also raises the question of whether demonstration of assay sensitivity in terms of LPV at the Day 5 evening time point with the active control DPH is the same as, i.e., does it necessarily establish, assay sensitivity at the Day 6 morning timepoint (or midday timepoint), the study time when the experimental drug would be more likely to affect driving safety if it has such an effect.

## **5.2 Conclusions and Recommendations**

An earlier parallel group driving safety study, XP083, using 1200 mg and 1800 mg Gabapentin Encarbil doses, higher than the recommended dose for restless leg syndrome, as well as diphenhydramine 50 mg showed some statistically significant effects on driving safety of these doses compared to placebo. However, the lower dose surprisingly showed more consistent effects in that study and even the low dose was higher than the recommended dose for the indication of restless leg syndrome associated with the related NDA. Therefore, a post marketing driving safety study was done in a healthy population to investigate the recommended dose for Restless leg syndrome and this latter study is the basis for this supplement. This study which utilized a 3 period, 3 treatment crossover design showed an effect of the active control, Diphenhydramine 50 mg, in the Evening on Day 5 in terms of the standard deviation of lane position on the road (LPV) in the simulated driving test, but no significant effects of Gabapentin encarbil compared to placebo at the three scheduled assessment times: Day 5 evening, Day 6 morning and Day 6 Midday on the prespecified driving safety measures. The study demonstrated assay sensitivity of the active control as planned due to practical limitations at a different time than an effect would be expected for Gabapentin due to different pharmacokinetic properties of the drugs. However, because it was done in the healthy population it still seems somewhat uncertain whether this recommended dose affects driving safety in the Restless Leg Syndrome population associated with the NDA. Also, the study did not demonstrate equivalence of placebo and Gabapentin rather it failed to detect a significant difference on the primary endpoint, standard deviation of linear position. This does not rule out a smaller (than Diphenhydramine 50 mg) but still important worsening effect of Gabapentin on driving safety compared to placebo, so it does not establish equivalence of Gabapentin and placebo. If feasible an equivalence or noninferiority design would have been more appropriate for a study question such as this since the sponsor's goal was to show "equivalence" to placebo in terms of driving safety. Also, here the question remains is 50 mg diphenhydramine the smallest dose that could have served as the

active control, i.e., have the desired safety effect. If not, then we cannot be sure that the absence of an observed significant driving effect of Gabapentin compared to placebo on the primary endpoint isn't still a study power issue. There were also numerically more simulated crashes in the Gabapentin group on Day 6 Midday than there were on Placebo at the same time (3 vs. 0). This result was not the primary endpoint and it was not nominally statistically significant but it was almost identical to the crash results for the active control, DPH, on Day 5 Evening which was, however, also not statistically significant. The study may not have been adequately powered to detect an effect on the secondary endpoint of crashes. Despite the lack of statistical significance the trend towards more simulated crashes on Gabapentin than placebo may still be worrisome due to the serious implications for public safety that such an effect would have.

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

/s/  
-----

TRISTAN S MASSIE  
09/17/2012

KUN JIN  
09/18/2012  
I concur with the review.

HSIEN MING J HUNG  
09/19/2012

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022399Orig1s005**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

# Clinical Pharmacology Review

## PMR REVIEW

---

---

PRODUCT (Generic Name):	Gabapentin Enacarbil
PRODUCT (Brand Name):	HORIZANT
DOSAGE FORM:	Extended-Release (ER) Tablets
DOSAGE STRENGTHS:	300 and 600 mg
NDA:	22399 (093)
INDICATION:	Restless Leg Syndrome
SUBMISSION DATES:	2/29/12
SPONSOR:	GSK
REVIEWER:	Veneeta Tandon, Ph.D.
PHARMACOMETRICS REVIEWER:	Atul Bhattaram, Ph.D.
PHARMACOMETRICS TEAM LEADER:	Atul Bhattaram, Ph.D.
SECONDARY REVIEWER:	Ta-Chen Wu, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

---

---

### TABLE OF CONTENTS

EXECUTIVE SUMMARY .....	2
RECOMMENDATION .....	5
LABELING RECOMMENDATIONS .....	6
DRUG-DRUG INTERACTION STUDY.....	7
Study RXP115720 .....	7
SIMULATED DRIVING STUDY .....	19
Study RXP114111 .....	19

## EXECUTIVE SUMMARY

Gabapentin enacarbil (GEN; HORIZANT® Extended-Release Tablets) was approved for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults on April 6, 2011.

This Prior Approval Supplement dated February 29, 2012 provides changes to the labeling based on two PMR studies: a simulated driving study (Protocol RXP114111) with 600 mg/day gabapentin enacarbil (PMR# 1588-7) and a morphine drug interaction study (Protocol RXP115720) (PMR# 1588-10).

The simulated driving study was reviewed by Dr. Atul Bhattaram and the morphine drug interaction study was reviewed by Dr. Veneeta Tandon.

**Simulated Driving Study:** Relationship between gabapentin concentrations and lane position variability, number of crashes was evaluated. The data did not suggest a relationship between gabapentin concentrations and changes in lane position variability, number of crashes.

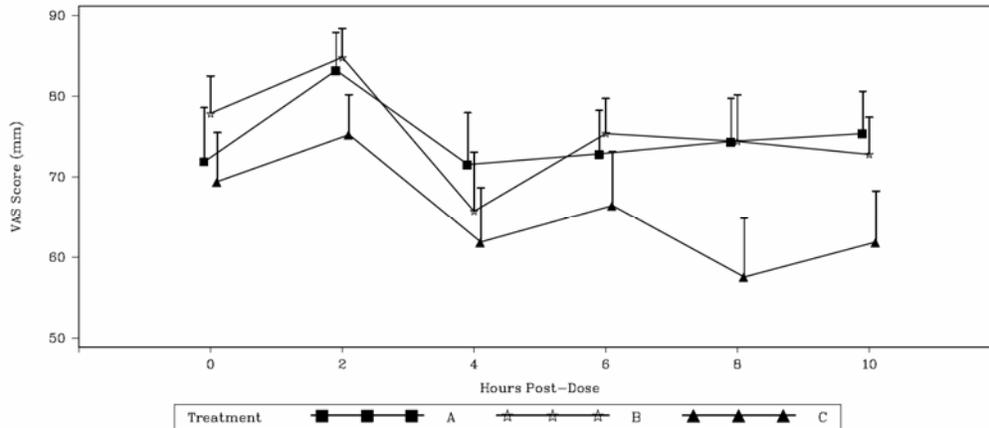
**Morphine Drug Interaction Study:** In a double-blind, 3-part crossover study to assess the pharmacokinetics and tolerability of single doses of 600-mg GEN and 60-mg morphine in 18 healthy male subjects, no pharmacokinetic interaction was observed between GEN and morphine. No changes in AUC<sub>0-t</sub> and C<sub>max</sub> of gabapentin enacarbil, morphine and its metabolite morphine-6-glucuronide were observed when GEN and morphine were co-administered compared to morphine alone as shown in the following Table. The confidence intervals were close and there were no significant outliers.

Parameter	Ratio (Combination/Alone) (90% CI)		
	GEN	Morphine	Morphine-6-glucuronide
AUC <sub>t</sub> (ng h/mL)	1.10 (1.03-1.16)	1.06 (1.1-1.09)	0.99 (0.92-1.05)
C <sub>max</sub> (ng/mL)	1.02 (0.92-1.12)	1.05 (0.97-1.13)	0.95 (0.85-1.06)

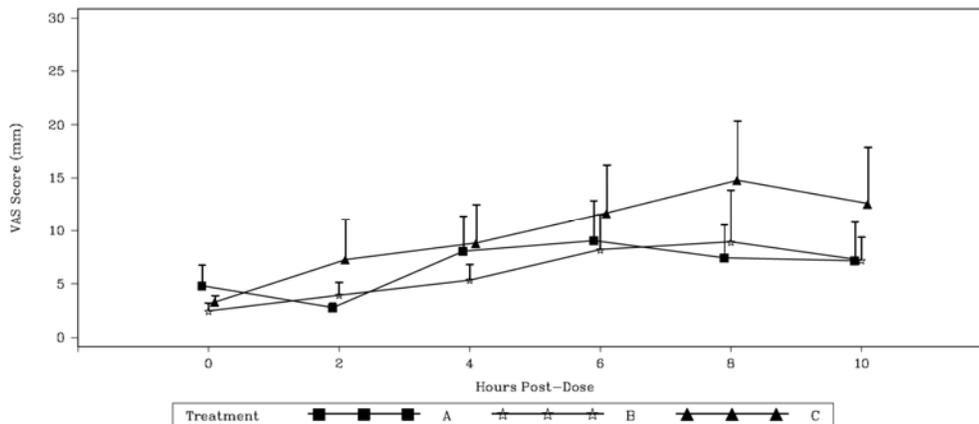
The sponsor believes that there was no evidence of a PD interaction as well between GEN and morphine as measured by Visual Analogue Scale (VAS scores) for somnolence/sedation, dizziness, and nausea. The sponsor concludes that the totality of the VAS data for somnolence/sedation, dizziness and nausea shows that the mean treatment differences between morphine administered alone and with GEN were similar, suggesting that there was no increase in symptom severity on co-administration. The sponsor tends to discuss the differences/similarities based on the comparison between morphine alone and GEN+ morphine in their discussions, although statistical comparisons of all arms have been conducted and presented in the study report. Clearly, the effect of morphine on GEN is more of our concern. As shown in the Figures below, there appears to be a trend of an additive effect on somnolence, dizziness and nausea when GEN is co-administered with morphine as compared to GEN alone, but this difference is not statistically different,

except at 8 hours post-dose. The maximum effect on somnolence/sedation, dizziness and nausea is observed around the Tmax of GEN administered 2 hours after the morphine dose. The sample size of this study is small to detect statistically significant changes in the VAS scores for sedation, dizziness and nausea, but nevertheless, additive effect of sedation, dizziness and nausea is observed when morphine and GEN are co-administered. Given that this was observed in a small study of 18 subjects, this additive effect may be multiplied when given to larger number of patients.

**Mean (SE) Somnolence/Sedation VAS over time**



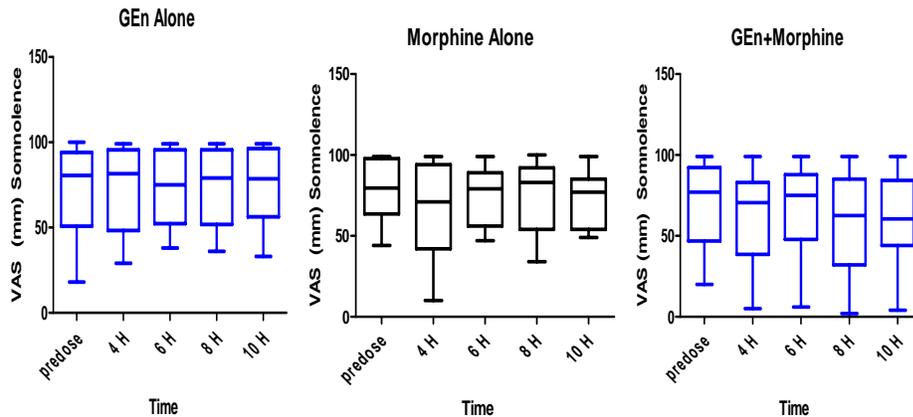
**Mean (SE) Dizziness VAS over time**



Treatment A: GEN alone; Treatment B: Morphine alone; Treatment C: GEN+Morphine

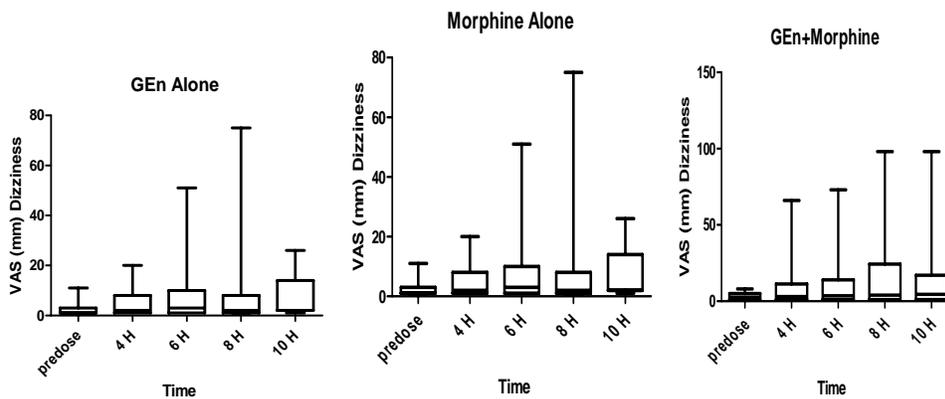
Box and Wiskers Plots showing the spread of the somnolence/sedation VAS data are given below. Although the mean VAS not significantly changed, it clearly shows that the GEN+morphine group has more subjects with lower VAS scores signifying increase in somnolence and sedation. The 2-hour time data was not plotted in this figure as that was the time when GEN was administered to all subjects. Increase in alertness was observed at

this time point. This time point is confounded by the fact that drug was administered at this time. Two subjects (2/18) had low VAS scores between 2-7 mm, suggesting complete somnolence/sedation.



Note: Lower scores signifying more sedation (VAS Scale 1-100 mm)

Box and Wiskers Plots showing the spread of the dizziness VAS data are presented below. The GEn+morphine group had more subjects with higher VAS scores, signifying increase in dizziness. Similar additive effects were also observed with nausea (see Individual Study Review).



Note: Higher scores signifying more Dizziness (VAS Scale 1-100 mm)

In the co-medication group, one subject (1/18) almost had a VAS score of 100 mm. This subject was highly sedated too. The AUC and Cmax of this subject were not high.

Given the trend, morphine should not be co-administered with GEn and the additive effects should be described in the label.

## RECOMMENDATION

The sponsor has fulfilled the following PMRs:

PMR 1588-10: A clinical drug-drug interaction trial to evaluate the pharmacokinetic and the pharmacodynamic interaction between gabapentin enacarbil and morphine (final report submission 4/2012).

PMR 1588-7 A simulated driving trial in healthy adult subjects treated with 600 mg gabapentin enacarbil that includes active comparator and placebo arms (Final report submission 2/2012)

The labeling changes in section 12.3 are given on page 3 of this review and should be conveyed to the sponsor. Reviewer changes (additions and deletions) are shown in yellow and blue highlight. The sponsor's changes are shown by track changes.

Veneeta Tandon, Ph.D.  
Division of Clinical Pharmacology I

Atul Bhattaram, Ph. D.  
Team Leader (Acting), Pharmacometrics,

Ta-Chen Wu, Ph.D.  
Team Leader (Acting), Division of Clinical Pharmacology I

## DRUG-DRUG INTERACTION STUDY

<b>Study RXP115720</b>	A Double-Blind, 3-Part Crossover Study to Assess the Pharmacokinetics and Tolerability of Single Doses of Gabapentin Enacarbil and Morphine
Rationale	<p>In a study exploring the analgesic effect of morphine in combination with oral gabapentin, a PK and PD effect was noted [Eckhardt, 2000]. Twelve healthy male subjects received a 60 mg oral dose of morphine followed 2 hours later by a 600 mg oral dose of gabapentin. The data showed a significant increase in pain tolerance (cold pressor test) with co-administration of both drugs compared with morphine administered alone.</p> <p>The pharmacokinetics of morphine and its glucuronide metabolites were not affected by gabapentin, but a 44% increase in gabapentin exposure (AUC) was noted when administered in combination with morphine. The most frequent side effects were somnolence, dizziness, and nausea. The sum of the AUC from time 0 to 6 hours after dosing was not significantly different for morphine plus gabapentin compared with morphine alone.</p> <p>The aim of the current study was to assess whether there was any PK or PD interaction between GEN and morphine.</p>
Study Design	<p>This was a single-center, double-blind, randomized, 3-part crossover study designed to evaluate the pharmacokinetics, tolerability, pharmacodynamics and safety of GEN when administered in combination with morphine in healthy adult male subjects.</p> <p>Screening Period (Days -28 to -1),          3 Treatment Periods at least 7 days apart (Days 1 and 2; dosing on Day 1 only in each period), and          Follow-up Visit that occurred 7 to 14 days after the last dose of study drug in Period 3.</p> <p>Total duration study: 8 weeks</p>
Study Population	<p>N=18 Healthy subjects          Age: 18-65 years          Gender: All males          Race: 8 White, 7 Black and 1 Asian, 2 Other</p>
Treatment Groups	<p><u>Treatment A:</u> morphine placebo+GEN 600 mg  <u>Treatment B:</u> morphine 60 mg+GEN placebo  <u>Treatment C:</u> morphine 60 mg+GEN 600 mg          Washout: 7 days between treatments</p>
Dosage and Administration	<p><u>Morphine Dose:</u> 60 mg Capsule          Administration: Administered at 8 am after a overnight fast          Batch number: 233D11          As it was not possible to provide fully matched morphine placebo,</p>

	<p>subjects were blindfolded for administration of morphine or morphine placebo.</p> <p>GEn dose: 600 mg ER Tablet Administration: at 10 am, 2 hours after the morphine administration in a fed state Batch number: 091209735</p>																												
Sampling: Blood	<p>For plasma gabapentin, morphine, and morphine-6<math>\beta</math>-glucuronide concentrations: Plasma samples were collected at predose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 12, 14, 16, 18, 20, 24, 26, and 36 hours post-dose</p>																												
Urine	none																												
Feces	none																												
Analysis	Plasma: The assay validation is acceptable																												
	<table border="1"> <thead> <tr> <th></th> <th>Gabapentine Enacabril</th> <th>Morphine</th> <th>Morphine-6<math>\beta</math>- glucuronide</th> </tr> </thead> <tbody> <tr> <td>Method</td> <td>LC/MS/MS</td> <td>LC/MS/MS</td> <td>LC/MS/MS</td> </tr> <tr> <td>Linear Range</td> <td>50-50000 ng/mL</td> <td>0.500-50.0 ng/mL</td> <td>0.5-50, 2-200 and 10-1000 ng/mL</td> </tr> <tr> <td>LLOQ</td> <td>50 ng/ml</td> <td>0.5 ng/mL</td> <td>0.5 and 2 ng/mL</td> </tr> <tr> <td>QCs</td> <td>50.0, 150, 400, 1500, 6000, and 37500 ng/mL.</td> <td>0.500, 1.00, 2.00, 5.00, 12.5, and 37.5 ng/mL</td> <td>1, 2, 5, 12, 40 ng/mL and 4, 8, 20, 50 and 150 ng/mL and 10.0, 20.0, 40.0, 100, 250, and 750 ng/mL</td> </tr> <tr> <td>Interday Precision</td> <td>% CV &lt;10.3</td> <td>% CV &lt;3.84</td> <td>% CV &lt;3.61</td> </tr> <tr> <td>Interday Accuracy (% diff from theoretical)</td> <td>-2.58 to -0.689</td> <td>1.31 to 6.31</td> <td>-0.364 to 1.64</td> </tr> </tbody> </table>		Gabapentine Enacabril	Morphine	Morphine-6 $\beta$ - glucuronide	Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	Linear Range	50-50000 ng/mL	0.500-50.0 ng/mL	0.5-50, 2-200 and 10-1000 ng/mL	LLOQ	50 ng/ml	0.5 ng/mL	0.5 and 2 ng/mL	QCs	50.0, 150, 400, 1500, 6000, and 37500 ng/mL.	0.500, 1.00, 2.00, 5.00, 12.5, and 37.5 ng/mL	1, 2, 5, 12, 40 ng/mL and 4, 8, 20, 50 and 150 ng/mL and 10.0, 20.0, 40.0, 100, 250, and 750 ng/mL	Interday Precision	% CV <10.3	% CV <3.84	% CV <3.61	Interday Accuracy (% diff from theoretical)	-2.58 to -0.689	1.31 to 6.31	-0.364 to 1.64
		Gabapentine Enacabril	Morphine	Morphine-6 $\beta$ - glucuronide																									
	Method	LC/MS/MS	LC/MS/MS	LC/MS/MS																									
	Linear Range	50-50000 ng/mL	0.500-50.0 ng/mL	0.5-50, 2-200 and 10-1000 ng/mL																									
	LLOQ	50 ng/ml	0.5 ng/mL	0.5 and 2 ng/mL																									
	QCs	50.0, 150, 400, 1500, 6000, and 37500 ng/mL.	0.500, 1.00, 2.00, 5.00, 12.5, and 37.5 ng/mL	1, 2, 5, 12, 40 ng/mL and 4, 8, 20, 50 and 150 ng/mL and 10.0, 20.0, 40.0, 100, 250, and 750 ng/mL																									
	Interday Precision	% CV <10.3	% CV <3.84	% CV <3.61																									
Interday Accuracy (% diff from theoretical)	-2.58 to -0.689	1.31 to 6.31	-0.364 to 1.64																										
PK Assessment	Cmax, AUC, AUCinf, Tmax, t1/2 of GEn, morphine and morphine-6-glucuronide																												
Safety Assessment	Clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), vital sign and pulse oximetry measurements, physical examination findings, the Columbia-Suicide Severity Rating Scale (C-SSRS), and 12-lead electrocardiogram (ECG)																												
PD Assessment	Visual analogue scale (VAS) for adverse events (AEs) of somnolence/sedation, dizziness, and nausea at specified intervals through 10 hours. The 2-hour time point for the VAS corresponded to the time when GEn or GEn placebo was administered. The somnolence/sedation VAS was a scale from "extremely sleepy" to "extremely alert," with higher scores indicating more alertness and less																												

sleepiness. The dizziness VAS was a scale from "not dizzy" to "extremely dizzy," with higher scores indicating more dizziness. The nausea VAS was a scale from "not nauseous" to "nauseous," with higher scores indicating more nausea. Each scale was 100 mm in length; the score was the distance in mm from the left hand anchor.

Pharmacokinetic Results: **GABAPENTIN ENACARBIL (GEn) + MORPHINE**

**Gabapentin:**

Peak mean plasma concentrations of gabapentin occurred approximately 7.5 hours [after GEn was administered alone and at approximately 6 hours after GEn was administered in combination with morphine. Thereafter, the plasma concentrations declined mono-exponentially.

**Summary of Derived Gabapentin Plasma Pharmacokinetic Parameters**

Parameter (unit)	GEn 600 mg N=16 <sup>a</sup>	GEn 600 mg + Morphine ER 60 mg N=18
AUC <sub>0-t</sub> (h•ng/mL) <sup>b</sup>	36400 (14.5)	39700 (12.1)
AUC <sub>0-inf</sub> (h•ng/mL) <sup>b</sup>	37700 (14.9)	41100 (12.9)
C <sub>max</sub> (ng/mL) <sup>b</sup>	3310 (15.3)	3370 (17.2)
t <sub>max</sub> (h) <sup>c</sup>	7.50 (4.03, 12.0)	6.00 (4.00, 12.0)
t <sub>1/2</sub> (h) <sup>b</sup>	5.93 (8.0)	5.96 (9.2)
CL/F (L/h) <sup>b</sup>	15.9 (14.9)	14.6 (12.9)
V <sub>z</sub> /F (L) <sup>b</sup>	136 (17.0)	125 (10.3)

For Treatment A, n=16 because Subjects (b) (6) were discontinued from the study.

b. Geometric mean (geometric %CV)<sup>b</sup> c. Median (minimum, maximum)

**Summary Results of the Statistical Analysis of Gabapentin Plasma Pharmacokinetic Parameters**

Parameter (unit)	Treatment <sup>a</sup>	n <sup>b</sup>	Geometric LS Means	Ratio of Geometric LS Means (C/A)	90% CI of the Ratio (C/A)
AUC <sub>0-inf</sub> (h•ng/mL)	A	16	37500	1.10	1.035–1.162
	C	18	41100		
C <sub>max</sub> (ng/mL)	A	16	3310	1.02	0.920–1.126
	C	18	3370		

The 90% CIs of the GLS mean ratios were entirely contained within the interval of 0.80 to 1.25, generally accepted as equivalent, suggesting no clinically relevant drug interaction effect due to morphine on the AUC<sub>0-inf</sub> or C<sub>max</sub> of gabapentin.

**Morphine:**

**Summary of Derived Morphine Plasma Pharmacokinetic Parameters**

Parameter (unit)	Morphine ER 60 mg N=15 <sup>a</sup>	GEn 600 mg + Morphine ER 60 mg N=18
AUC <sub>0-t</sub> (h•ng/mL) <sup>b</sup>	146 (24.9)	147 (28.4)
AUC <sub>0-inf</sub> (h•ng/mL) <sup>b</sup>	208 (6.8) <sup>e</sup>	129 (-) <sup>f</sup>
C <sub>max</sub> (ng/mL) <sup>b</sup>	7.47 (30.3)	7.37 (40.0)

%AUCex (%) <sup>c</sup>	25.8 (9.36) <sup>g</sup>	26.5 (9.11) <sup>h</sup>
tmax (h) <sup>d</sup>	11.0 (1.07, 18.0)	14.0 (7.00, 18.0)
t1/2 (h) <sup>b</sup>	14.6 (33.1) <sup>g</sup>	15.2 (41.0) <sup>h</sup>
AUC0-t (h•ng/mL) <sup>b</sup>	146 (24.9)	147 (28.4)

For morphine ER 60 mg, n=15 because Subjects (b) (6) were discontinued from the study.

b. Geometric mean (geometric %CV)<sup>b</sup> c. Arithmetic Mean (SD) d. Median (minimum, maximum)  
e. n=2 f. n=1 h. n=7 g. n=6

The percent of AUC0-inf extrapolated beyond the last quantifiable concentration (%AUCex [%]) was greater than 20% in most cases for morphine and morphine-6-glucuronide. Therefore, AUC0-inf was not retained in most cases and no statistical comparisons were performed for AUC0-inf due to the small sample sizes.

### Summary Results of the Statistical Analysis of Morphine Plasma

#### Pharmacokinetic Parameters

Parameter (unit)	Treatment <sup>a</sup>	n <sup>b</sup>	Geometric LS Means	Ratio of Geometric LS Means (C/B)	90% CI of the Ratio (C/B)
AUC0-t (h•ng/mL)	B	15	139	1.06	1.014–1.098
	C	18	147		
Cmax (ng/mL)	B	15	7.04	1.05	0.967–1.134
	C	18	7.37		

The 90% CIs of the GLS mean ratios were entirely contained within the interval of 0.80 to 1.25, generally accepted as equivalent, suggesting no clinically relevant drug interaction effect due to GEN on the AUC0-inf or Cmax of morphine.

### Morphine-6-glucuronide:

#### Summary of Derived Morphine-6-Glucuronide Plasma Pharmacokinetic Parameters

Parameter (unit)	Morphine ER 60 mg N=15 <sup>a</sup>	GEN 600 mg + Morphine ER 60 mg N=18
AUC0-t (h•ng/mL) <sup>b</sup>	899 (14.8)	873 (19.6)
AUC0-inf (h•ng/mL) <sup>b</sup>	1094 (15.4) <sup>e</sup>	896 (–) <sup>f</sup>
Cmax (ng/mL) <sup>b</sup>	51.0 (22.1)	47.9 (33.3)
%AUCex (%) <sup>c</sup>	20.4 (9.12) <sup>g</sup>	24.3 (5.84) <sup>h</sup>
tmax (h) <sup>d</sup>	12.0 (1.95, 18.0)	11.0 (6.00, 16.0)
t1/2 (h) <sup>b</sup>	12.6 (38.3) <sup>g</sup>	14.6 (20.7) <sup>h</sup>
AUC0-t (h•ng/mL) <sup>b</sup>	899 (14.8)	873 (19.6)

a. For morphine ER 60 mg, n=15 because Subjects (b) (6) were discontinued from the study.

b. Geometric mean (geometric %CV)<sup>b</sup> c. Arithmetic Mean (SD) d. Median (minimum, maximum)  
e. n=5 f. n=1 g. n=11 h. n=12

For most of these subjects, AUC0-inf was not reported due to a fraction extrapolated greater than 20%.

### Summary Results of the Statistical Analysis of Morphine-6-Glucuronide Plasma

#### Pharmacokinetic Parameters

Parameter (unit)	Treatment <sup>a</sup>	n <sup>b</sup>	Geometric LS Means	Ratio of Geometric LS Means (C/B)	90% CI of the Ratio (C/B)
AUC <sub>0-t</sub> (h•ng/mL)	B	15	880	0.992	0.929–1.058
	C	18	873		
C <sub>max</sub> (ng/mL)	B	15	50.3	0.953	0.855–1.062
	C	18	47.9		

The 90% CIs of the GLS mean ratios were entirely contained within the interval of 0.80 to 1.25, generally accepted as equivalent.

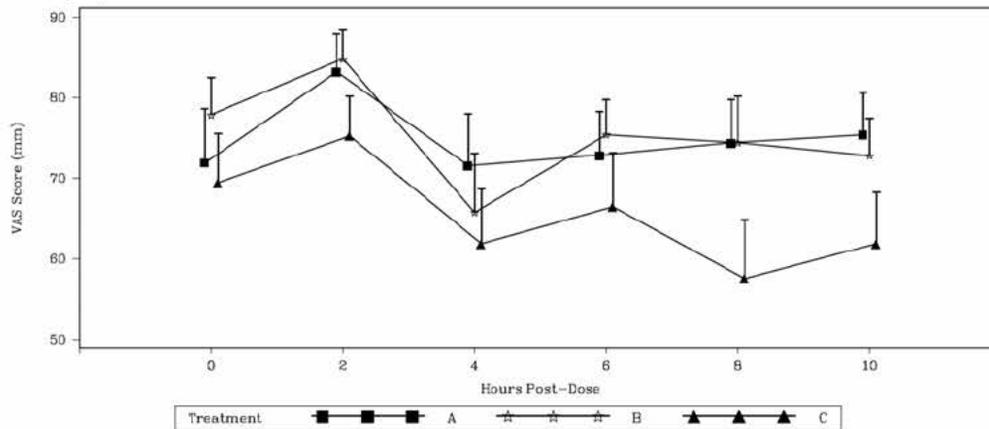
Pharmacodynamics

**VAS SCORES FOR SOMNOLENCE, DIZZINESS AND NAUSEA**

**Somnolence/Sedation:**

For the somnolence/sedation VAS, higher scores indicated more alertness and less sleepiness. Therefore, a decrease in VAS score from before to after dosing indicated more sleepiness and an increase from before to after dosing indicated an increase in alertness and less sleepiness.

**Mean (SE) Somnolence/Sedation VAS over time**



Compared with Baseline, a small increase in alertness was observed at the 2-hour assessment in all 3 treatment periods corresponding to the time at which GEN was administered 2 hours after morphine dosing, hence this time point is of little relevance. In the periods when morphine and GEN (Treatment C) were administered, the assessments from 4 to 10 hours after the morphine dose showed a trend for greater sleepiness when the GEN alone arm (Treatment A).

**Summary of VAS:**

Treatment	N	Relative Time	n	Mean	SD
Morphine placebo + GEn 600 mg	16	Baseline	16	71.9	26.82
		2 H	16	83.2	18.79
		4 H	16	71.5	25.94
		6 H	16	72.8	21.83
		8 H	16	74.4	21.45
		10 H	16	75.4	21.08
Morphine ER 60 mg + GEn placebo	15	Baseline	15	80.1	16.87
		2 H	15	84.8	13.98
		4 H	15	65.7	28.38
		6 H	15	75.4	16.56
		8 H	15	74.4	22.14
		10 H	15	72.8	17.93
Morphine ER 60 mg + GEn 600 mg	18	Baseline	18	69.4	26.02
		2 H	18	75.2	21.20
		4 H	18	61.8	28.99
		6 H	18	66.4	28.49
		8 H	18	57.6	30.89
		10 H	18	61.8	27.06

**Summary of Change from Baseline:**

Treatment	N	Relative Time	n	Mean	SD
Morphine placebo + GEn 600 mg	16	Baseline	16	71.9	26.82
		2 H	16	11.3	12.75
		4 H	16	-0.4	19.41
		6 H	16	0.9	21.08
		8 H	16	2.5	25.41
		10 H	16	3.5	26.81
Morphine ER 60 mg + GEn placebo	15	Baseline	15	80.1	16.87
		2 H	15	4.7	10.72
		4 H	15	-14.4	27.14
		6 H	15	-4.7	15.06
		8 H	15	-5.7	18.66
		10 H	15	-7.3	15.58
Morphine ER 60 mg + GEn 600 mg	18	Baseline	18	69.4	26.02
		2 H	18	5.8	15.00
		4 H	18	-7.6	23.44
		6 H	18	-2.9	23.90
		8 H	18	-11.8	35.34
		10 H	18	-7.6	30.46

These tables clearly show that the morphine+GEn arm showed increased sedation, with the peak effect occurring at 8 hours post dose.

The ANOVA statistical analysis conducted by the sponsor is summarized below. Statistically significant evaluations of these pharmacodynamic endpoints given the small sample size should be viewed with caution. A trend towards increased sedation when GEn and morphine were co-administered is evident.

Based on the ANOVA analysis, there was a trend for a decrease in adjusted mean change from baseline somnolence/sedation scores during the GEn 600 mg/morphine 60 mg period versus the GEn 600 mg period, signifying increased sedation. It was at the 8-hour time point that the 90% CI for the difference did not include zero. The difference at this time point was -15.42 (90% CI: -29.69, -1.14). The difference in change from Baseline in mean

somnolence/sedation scores at 8 hours between the GEN 600 mg/morphine 60 mg period and the morphine 60 mg period was -10.53 (90% CI: -25.09, 4.03). This 8-hour time point coincides with the Tmax of GEN (6 hrs), when the maximum sedation was observed.

Symptom	Change from Baseline to:	Treatment <sup>a</sup>	n <sup>b</sup>	Adjusted Mean	SE of Adjusted Mean	Difference (C-A or C-B)	90% CI for Treatment Difference
Somnolence/sedation	2 hours	A	16	10.8	2.41	-6.56	(-11.50, -1.63)
		B	15	7.5	2.51	-3.26	(-8.39, 1.87)
		C	18	4.2	2.28		
	4 hours	A	16	-0.9	5.67	-8.26	(-21.11, 4.58)
		B	15	-11.6	5.87	2.42	(-10.69, 15.52)
		C	18	-9.2	5.35		
	6 hours	A	16	0.4	4.54	-4.96	(-15.13, 5.20)
		B	15	-1.9	4.70	-2.64	(-13.04, 7.76)
		C	18	-4.6	4.29		
	8 hours	A	16	2.0	6.28	-15.42	(-29.69, -1.14)
		B	15	-2.9	6.50	-10.53	(-25.09, 4.03)
		C	18	-13.5	5.93		
10 hours	A	16	3.0	5.52	-12.14	(-24.62, 0.34)	
	B	15	-4.5	5.71	-4.65	(-17.39, 8.09)	
	C	18	-9.2	5.21			

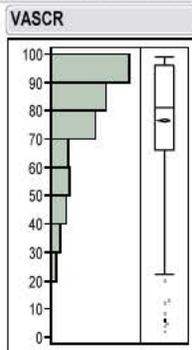
Treatment A=morphine placebo+GEN 600 mg

Treatment B=morphine 60 mg extended release+GEN placebo

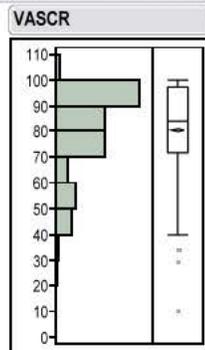
Treatment C=morphine 60 mg extended-release+GEN 600 mg extended-release

In addition, the distribution of VAS scores in the three groups is shown in the following figures. This shows that the GEN+ morphine group has the highest number of individual VAS scores that are very low (0-20) indicating increased somnolence.

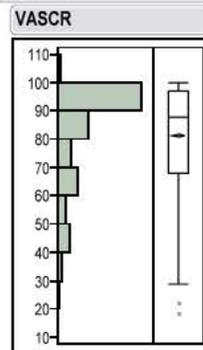
Distributions PRTTRGP=Morphine ER 60 mg + GEN 600 mg



Distributions PRTTRGP=Morphine ER 60 mg + GEN placebo



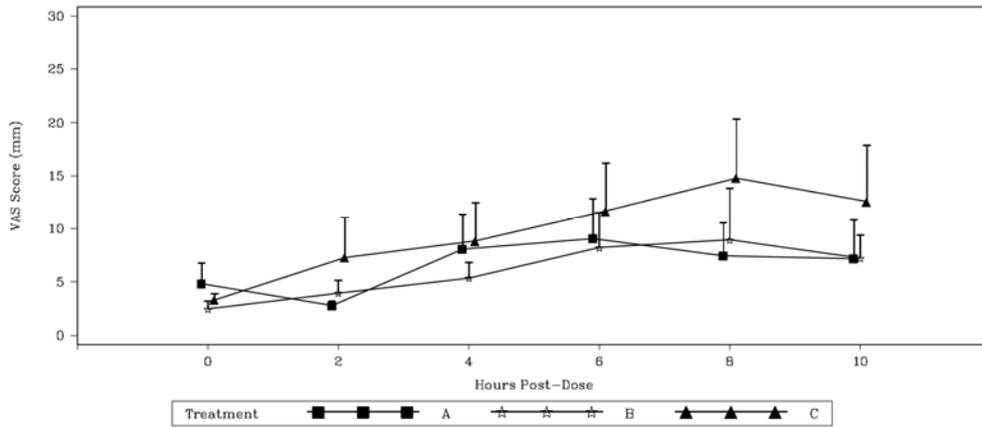
Distributions PRTTRGP=Morphine placebo + GEN 600 mg



**Dizziness:** For the dizziness VAS, higher scores indicated more dizziness. Therefore an increase from before to after dosing indicated an increase in dizziness. In this case also, the maximum dizziness was observed at the 8 hour time point and was highest in the group where

GEn and morphine were co administered as compared to the GEn alone group.

**Mean (SE) Dizziness VAS over time**



Symptom	Change from Baseline to:	Treatment <sup>a</sup>	n <sup>b</sup>	Adjusted Mean	SE of Adjusted Mean	Difference (C-A or C-B)	90% CI for Treatment Difference
Dizziness	2 hours	A	16	-1.1	3.49	4.84	(-0.86, 10.54)
		B	15	1.2	3.56	2.60	(-3.21, 8.40)
		C	18	3.8	3.37		
	4 hours	A	16	4.2	2.96	1.08	(-2.67, 4.83)
		B	15	2.6	3.00	2.75	(-1.07, 6.58)
		C	18	5.3	2.88		
	6 hours	A	16	5.2	3.30	2.91	(-2.20, 8.02)
		B	15	5.4	3.36	2.72	(-2.49, 7.93)
		C	18	8.2	3.19		
	8 hours	A	16	3.6	4.80	7.65	(-1.83, 17.13)
		B	15	6.2	4.92	5.10	(-4.55, 14.75)
		C	18	11.3	4.58		
10 hours	A	16	3.4	3.99	5.68	(-1.55, 12.91)	
	B	15	4.4	4.08	4.61	(-2.75, 11.97)	
	C	18	9.0	3.83			

Treatment A=morphine placebo+GEn 600 mg

Treatment B=morphine 60 mg extended release+GEn placebo

Treatment C=morphine 60 mg extended-release+GEn 600 mg extended-release

**Summary of VAS:**

Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Morphine placebo + GEn 600 mg	16	Baseline	16	4.8	7.74	2.0	1	30
		2 H	16	2.8	1.69	2.0	1	5
		4 H	16	8.1	13.12	2.5	1	53
		6 H	16	9.1	15.18	3.0	1	62
		8 H	16	7.4	12.64	2.5	1	51
		10 H	16	7.2	14.64	3.0	1	61
Morphine ER 60 mg + GEn placebo	15	Baseline	15	2.5	2.95	1.0	0	11
		2 H	15	3.9	4.50	2.0	1	15
		4 H	15	5.3	5.69	2.0	1	20
		6 H	15	8.2	12.81	3.0	1	51
		8 H	15	8.9	18.95	2.0	0	75
		10 H	15	7.2	8.44	2.0	1	26
Morphine ER 60 mg + GEn 600 mg	18	Baseline	18	3.3	2.56	2.5	0	8
		2 H	18	7.3	16.01	2.0	0	70
		4 H	18	8.8	15.35	3.0	0	66
		6 H	18	11.7	19.30	3.5	0	73
		8 H	18	14.8	23.57	4.0	1	98
		10 H	18	12.6	22.56	4.5	1	98

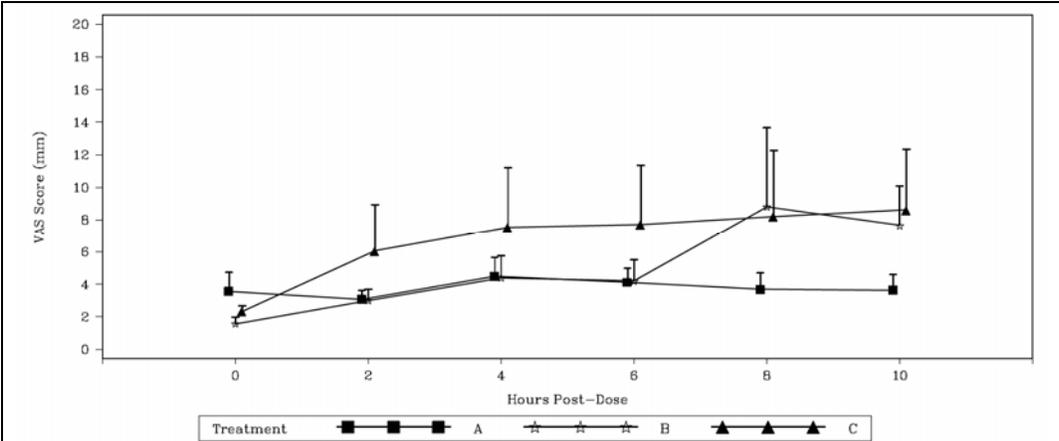
**Summary of Change from Baseline:**

Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Morphine placebo + GEn 600 mg	16	Baseline	16	4.8	7.74	2.0	1	30
		2 H	16	-2.1	7.16	0.0	-25	3
		4 H	16	3.3	13.97	0.5	-22	49
		6 H	16	4.3	17.45	0.0	-26	58
		8 H	16	2.6	14.65	0.0	-27	47
		10 H	16	2.4	16.33	0.0	-26	57
Morphine ER 60 mg + GEn placebo	15	Baseline	15	2.5	2.95	1.0	0	11
		2 H	15	1.4	4.27	1.0	-8	11
		4 H	15	2.8	6.32	2.0	-10	20
		6 H	15	5.7	13.58	1.0	-10	51
		8 H	15	6.4	19.36	0.0	-9	74
		10 H	15	4.7	8.58	1.0	-9	25
Morphine ER 60 mg + GEn 600 mg	18	Baseline	18	3.3	2.56	2.5	0	8
		2 H	18	4.0	15.32	0.0	-1	65
		4 H	18	5.6	14.92	0.0	-5	61
		6 H	18	8.4	18.94	0.5	-4	68
		8 H	18	11.5	22.70	1.5	-2	93
		10 H	18	9.3	22.15	0.5	-2	93

Similar trends towards increased dizziness in the Morphine+GEn treated arm was observed, with effects peaking around the Tmax of GEn.

**Nausea:** For the nausea VAS, higher scores indicated more nausea. Therefore an increase from before to after dosing indicated an increase in nausea. In this case also, the maximum nausea was observed at the 8 hour time point and was highest in the group where GEn and morphine were co administered as compared to the GEn alone group.

**Mean (SE) Nausea VAS over time**



**Summary of VAS:**

Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Morphine placebo + GEn 600 mg	16	Baseline	16	3.6	4.69	2.0	0	17
		2 H	16	-0.5	3.85	1.0	-13	4
		4 H	16	0.9	5.41	1.0	-10	14
		6 H	16	0.6	6.01	0.5	-15	10
		8 H	16	0.1	6.25	0.5	-15	14
		10 H	16	0.1	3.32	0.0	-9	6
Morphine ER 60 mg + GEn placebo	15	Baseline	15	1.6	1.72	1.0	0	7
		2 H	15	1.4	1.59	1.0	-1	5
		4 H	15	2.8	3.91	1.0	0	13
		6 H	15	2.6	3.96	1.0	0	13
		8 H	15	7.2	18.90	2.0	-2	74
		10 H	15	6.1	9.38	2.0	-1	32
Morphine ER 60 mg + GEn 600 mg	18	Baseline	18	2.3	1.50	2.0	1	7
		2 H	18	3.7	12.25	0.0	-1	52
		4 H	18	5.2	15.22	0.0	-2	64
		6 H	18	5.4	15.37	0.5	-1	65
		8 H	18	5.9	17.18	0.0	-2	69
		10 H	18	6.3	15.96	0.0	-2	64

Symptom	Change from Baseline to:	Treatment <sup>a</sup>	n <sup>b</sup>	Adjusted Mean	SE of Adjusted Mean	Difference (C-A or C-B)	90% CI for Treatment Difference
Nausea	2 hours	A	16	0.5	2.01	3.07	(-1.35, 7.50)
		B	15	0.6	2.07	2.96	(-1.50, 7.43)
		C	18	3.6	1.85		
	4 hours	A	16	1.9	2.61	3.14	(-2.73, 9.00)
		B	15	2.0	2.69	3.06	(-2.88, 9.01)
		C	18	5.1	2.43		
	6 hours	A	16	1.6	2.60	3.68	(-2.15, 9.51)
		B	15	1.8	2.68	3.43	(-2.48, 9.34)
		C	18	5.2	2.42		
	8 hours	A	16	1.1	3.76	4.62	(-3.95, 13.18)
		B	15	6.4	3.88	-0.67	(-9.37, 8.03)
		C	18	5.7	3.52		
10 hours	A	16	1.1	2.86	5.07	(-1.38, 11.52)	
	B	15	5.3	2.95	0.85	(-5.69, 7.39)	
	C	18	6.1	2.66			

Treatment A=morphine placebo+GEN 600 mg

Treatment B=morphine 60 mg extended release+GEN placebo

Treatment C=morphine 60 mg extended-release+GEN 600 mg extended-release

**Reviewer's Comment:** No pharmacokinetic interaction was observed between GEN and morphine. The sponsor believes that there was no evidence of a PD interaction as well between GEN and morphine as measured by VAS scores for somnolence/sedation, dizziness, and nausea. The sponsor concludes that the totality of the VAS data for somnolence/sedation, dizziness and nausea shows that the mean treatment differences between morphine administered alone and with GEN were similar, suggesting that there was no increase in symptom severity on coadministration. But the sponsor tends to discuss the differences/similarities based on the comparison between morphine alone and GEN+ morphine in their discussions, although statistical comparisons of all arms have been conducted. Clearly, the effect of morphine on GEN is more of our concern. There appears to be a trend of an additive effect on somnolence, dizziness and nausea when GEN is co-administered with morphine when compared to GEN alone, but this difference is not statistically different, except at 8 hrs post-dose. The maximum effect on somnolence/sedation, dizziness and nausea is observed around the T<sub>max</sub> of GEN. The sample size of this study is small to detect statistically significant changes in the VAS scores for sedation, dizziness and nausea, but nevertheless, an additive effect of sedation, dizziness and nausea is observed when morphine and GEN are co-administered. The clinical significance of a ~15 mm decrease in mean VAS scores suggesting increased sedation is not known. Given the trend, morphine should not be co-administered with GEN.

Safety	There were more AEs recorded when morphine was administered with GEN (any event 28%) than when GEN was administered alone (any event 13%).
Conclusion	<ul style="list-style-type: none"> <li>No PK drug interaction was observed between GEN and morphine.</li> <li>There was a trend towards an increase in somnolence/sedation, dizziness, and nausea as measured by VAS scores when GEN and morphine were co-administered compared to GEN alone, although the difference was statistically significant only at the peak concentrations.</li> </ul>

	of GEn. • There was no increase in the frequency or severity of AEs after administration of GEn in combination with morphine versus administration of morphine alone.
Dose Adjustment	Not recommended to coadminister GEn with morphine.

APPEARS THIS WAY ON ORIGINAL

## SIMULATED DRIVING STUDY

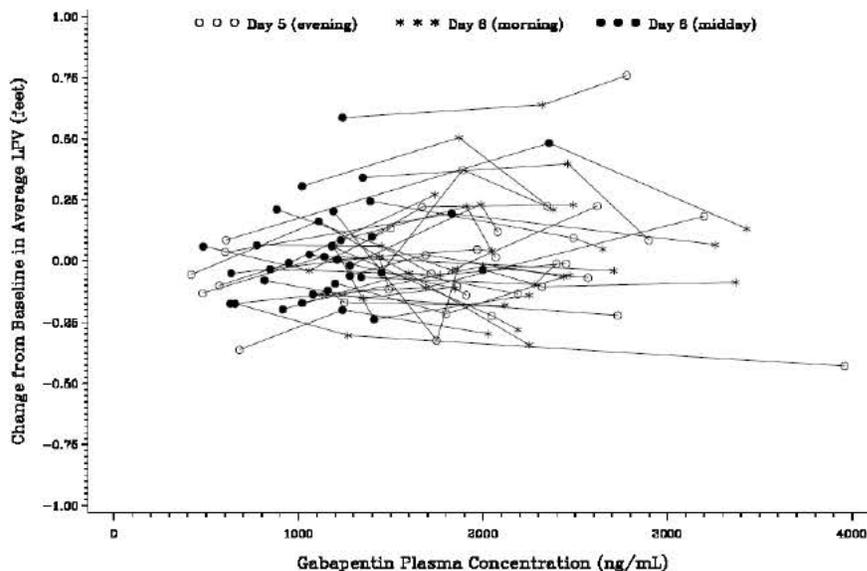
<b>Study RXP114111</b>	A Randomized, Double-Blind, Double-Dummy, Active- and Placebo-Controlled, Crossover Study Assessing the Effect of 600 mg Gabapentin Enacarbil (GEn) on Simulated Driving in Healthy Subjects
Rationale	In subjects with RLS, impairments in simulated driving ability were noted at GEn doses of 1200 and 1800 mg once daily following repeated dosing for 2 weeks (Previous parallel-group study (XP083)). The degree of impairment was similar to that following a single dose of 50 mg Diphenhydramine (DPH), which was administered as an active control. This present study was designed to assess the effect of GEn 600 mg once daily, the recommended dose for the treatment of RLS in adults, on simulated driving performance.
Study Design	Randomized, double-blind, double-dummy, active- and placebo-controlled, 3-period crossover study designed to assess the effect of GEn 600 mg on simulated driving performance in healthy adult subjects. Each subject participated in 3 dosing and simulated driving assessment periods.  The total duration of the subject's participation in the study was up to approximately 9 weeks, which included up to a 28-day Screening Period, three 6-day Treatment Periods, 2 additional washout days, and an approximately 14-day Follow-up Period.  Subjects received each of 3 treatments in a randomized sequence: placebo, GEn 600 mg, and DPH 50 mg
Study Population	N=36 Healthy subjects Age: 19-57 years Gender: 16 Female, 20 Male Race: 25 White, 9 African American and 1 Asian, 1 White and African American
Treatment Groups	A. Placebo B. GEn 600 mg C. DPH 50 mg
Dosage and Administration	<b>A. Placebo</b> GEn matching placebo + DPH matching placebo on Days 1 through 5 GEn matching placebo + DPH matching placebo on Day 6 <b>B. GEn 600 mg</b> GEn 600 mg + DPH matching placebo on Days 1 through 5 GEn matching placebo + DPH matching placebo on Day 6 <b>C. DPH 50 mg</b> GEn matching placebo + DPH matching placebo on Days 1 through 4 GEn matching placebo + DPH 50 mg on Day 5 GEn matching placebo + DPH matching placebo on Day 6

Sampling: Blood	Blood samples were collected after simulated driving tests were conducted. Simulated driving assessments were conducted approximately 2 to 4 hours after dosing on Day 5 (7 to 9 PM) and on the following morning (7 to 9 AM, approximately 14 to 16 hours after dosing) and at midday (11 AM to 1 PM, approximately 18 to 20 hours after dosing) on Day 6 of each treatment period.
PK Assessment	Concentrations of gabapentin at 2-4 hours, 14-16 hours and 18-20 hours post dosing.
Safety Assessment	Please refer to Medical Officer's review.
PD Assessment	Lane position variability (LPV), speed variability (SV), and the number of simulated crashes were calculated for each subject for each 60-minute driving simulation based on the data collected during the simulation.
PK/PD Results:	<b>Effect of Gabapentin on Lane Position Variability</b>

**Sponsor's Analysis**  
**Study RXP114111**

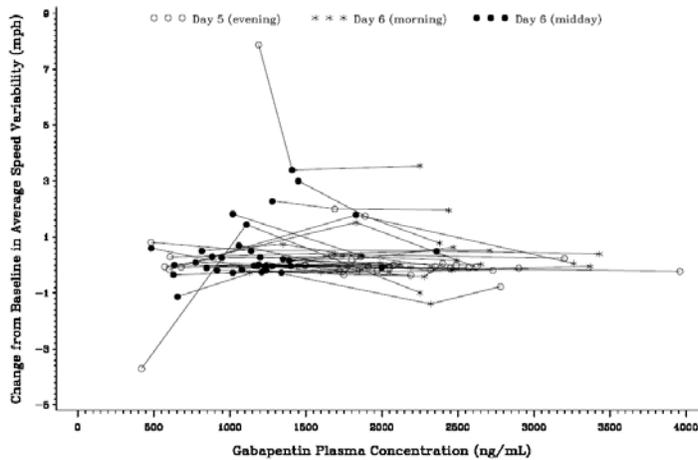
There was no apparent relationship between individual gabapentin plasma concentrations and individual change from baseline in mean LPV (See figure below).

**Gabapentin Plasma Concentration (ng/mL) Versus Change from Baseline in Mean Lane Position Variability (ft) (Pharmacokinetic Population)**



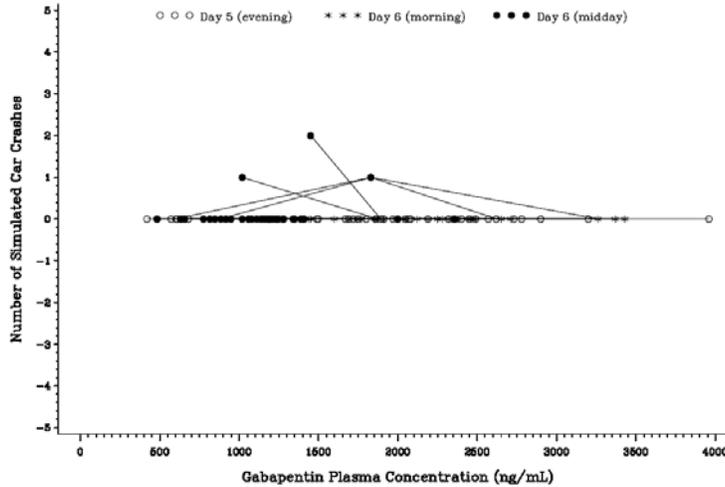
There was no apparent relationship between individual gabapentin plasma concentrations and individual change from baseline in mean speed variability (See figure below).

**Gabapentin Plasma Concentration (ng/mL) Versus Change from Baseline in Mean Speed Variability (mph) (Pharmacokinetic Population)**



There was no apparent relationship between individual gabapentin plasma concentrations and individual number of simulated driving crashes.

**Gabapentin Plasma Concentration (ng/mL) Versus Number of Simulated Driving Crashes (Pharmacokinetic Population)**



**Sponsor's Conclusion:**

The mean change from baseline in LPV and SV was not notably different between the GEN 600 mg and placebo treatment periods indicating a lack of effect of GEN on these simulated driving endpoints in this study. This lack of effect of GEN on driving

performance was seen at Day 5 evening (2 to 4 hours after dosing), Day 6 morning (14 to 16 hours after dosing), and Day 6 midday (18 to 20 hours after dosing) showing that GEN at this dose had no immediate or delayed effect on driving performance within this time frame.

**Reviewer's Analysis Relationship between gabapentin concentrations, lane position variability (LPV) and number of crashes in healthy subjects and patients with RLS (Restless Legs Syndrome)**

***Relationship between gabapentin concentrations and lane position variability (LPV)***

Figure below shows the relationship between gabapentin concentrations and changes in lane position variability in healthy subjects and RLS patients. For illustration purposes the reviewer created

- (A) 8 bins of gabapentin concentrations and
- (B) Plotted the mean change in baseline, placebo corrected lane position variability versus the mean gabapentin concentration in each bin.

**Gabapentin Plasma Concentration (ng/mL) Versus Baseline, Placebo Corrected Change in Lane Position Variability in RLS Patients (Left) and Healthy Subjects**

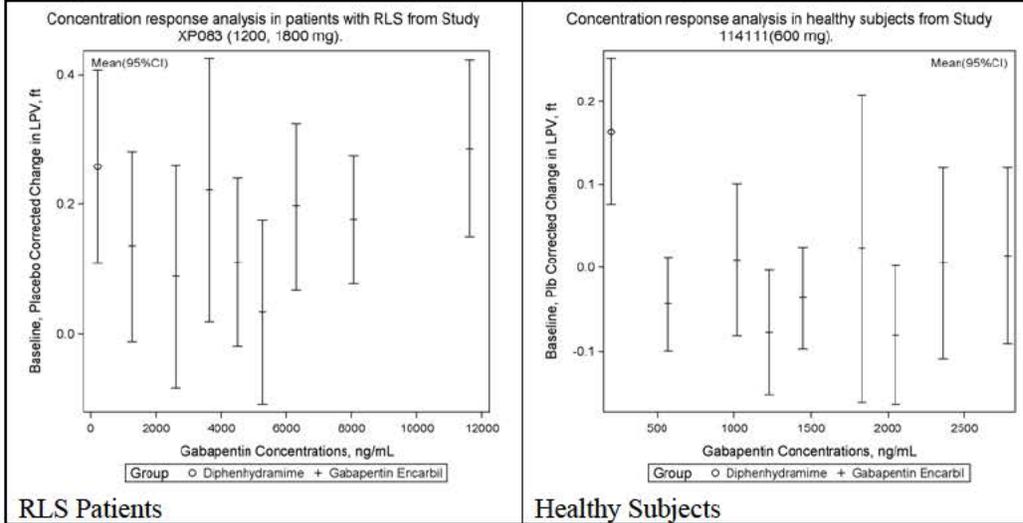
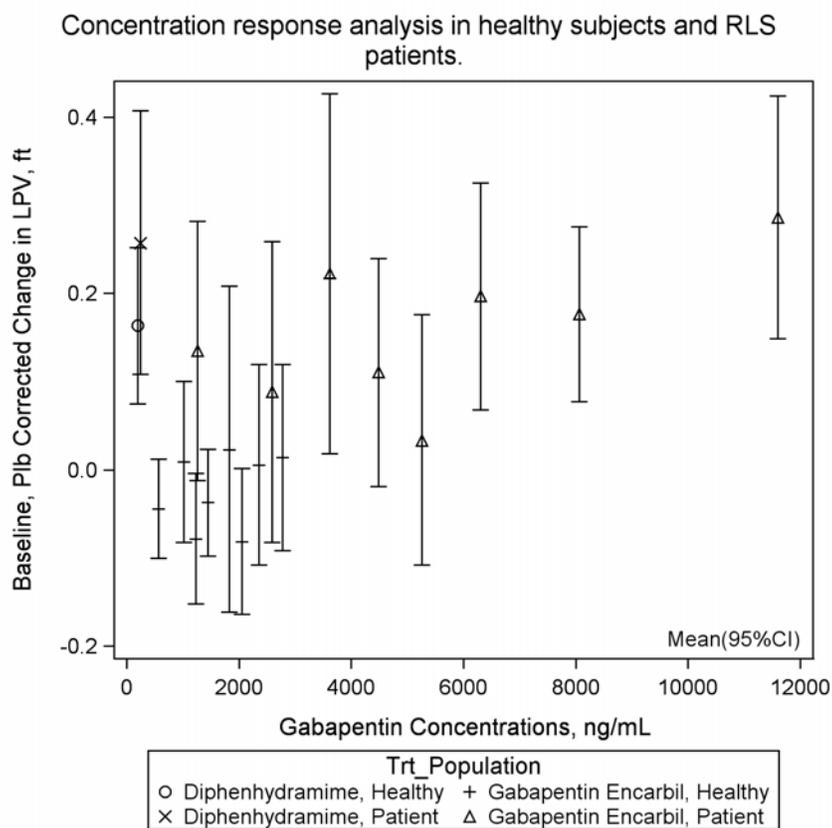


Figure below shows the overlay of the relationship between gabapentin concentrations and changes in LPV in healthy subjects and RLS patients.

**Gabapentin Plasma Concentration (ng/mL) Versus Baseline, Placebo Corrected Change in Lane Position Variability in RLS Patients and Healthy Subjects**



The peak (7h post dose) and next day morning gabapentin concentrations after 600, 1200 and 1800 mg are shown in table below. Also shown are the observed minimum and maximum gabapentin concentrations.

Dose	Gabapentin Concentrations (ng/mL)	
	7h post dose (Peak)	14h post dose (Next day morning)
600 mg	Not available. Assuming dose proportionality, the concentrations would be 3200	2084 (Min: 1060; Max 3430)
1200 mg	6355 (Min:656; Max 11500)	4257 (Min:180; Max 7770)
1800 mg	10082 (Min:4440; Max 19800)	5824 (Min:2460; Max 11800)

The figure above shows that baseline, placebo corrected changes in LPV are different for

diphenhydramine in the two studies. This could be due to two separate studies or study population (healthy vs RLS patients). The concentration-response relationship suggests that the changes in lane position variability, after administration of 600 mg, would be less when compared to diphenhydramine.

**Relationship between gabapentin concentrations and number of crashes**

Tables below show the mean, standard deviation(Std) and median gabapentin concentrations by overall number of crashes in the simulated driving study.

Crashes	Treatment Group							
	1200 mg				1800 mg			
	Gabapentin Concentration				Gabapentin Concentration			
	N	Mean	Std	Median	N	Mean	Std	Median
0	60	4253.45	2495.20	4035.00	89	6107.35	3718.28	5200.00
1	10	4691.00	2437.41	4275.00	4	9062.50	4313.18	8145.00
2	5	2768.00	1475.46	3430.00	.	.	.	.
3	1	3340.00	.	3340.00	3	10143.33	3886.98	10000.00
4	4	5687.50	2970.05	6755.00	.	.	.	.
5	1	1220.00	.	1220.00	.	.	.	.
13	2	4075.00	2439.52	4075.00	1	13000.00	.	13000.00
17	1	5260.00	.	5260.00	.	.	.	.

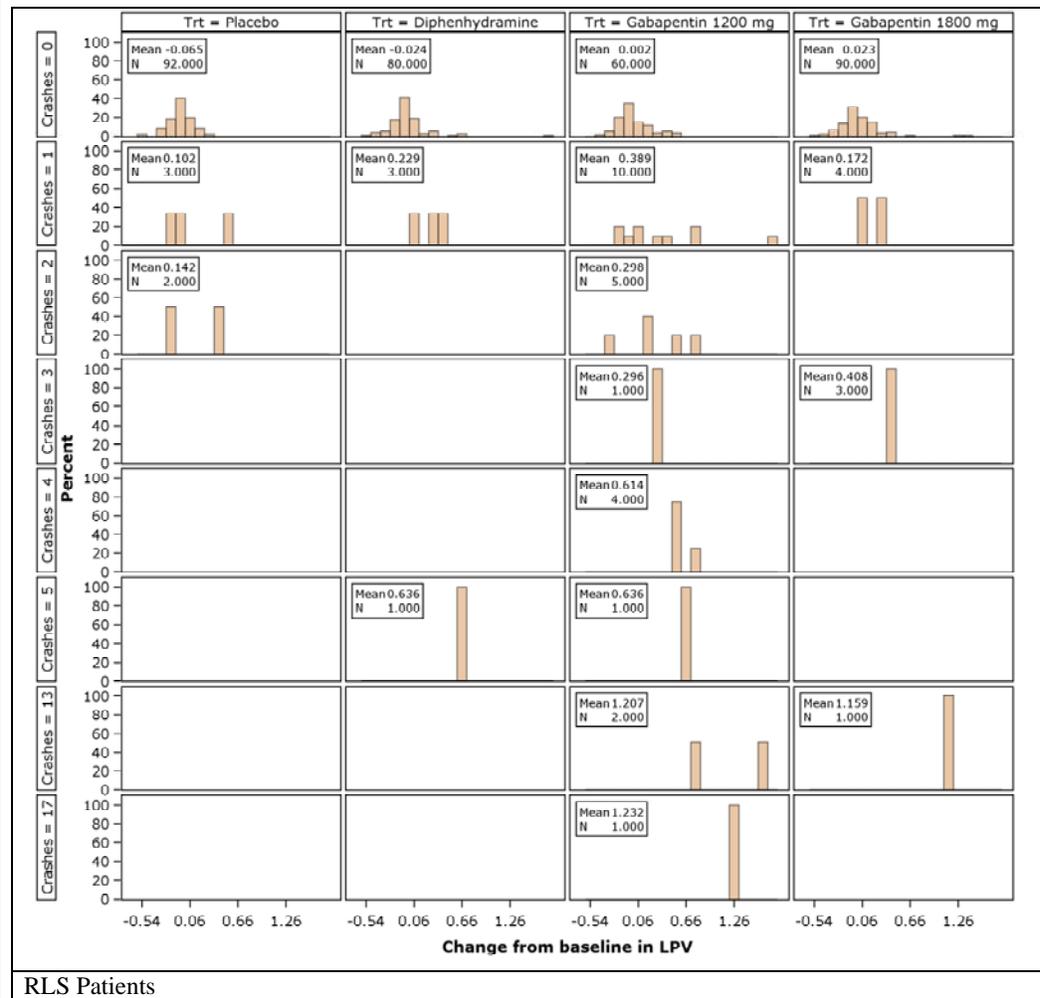
Crashes	Treatment Group			
	GEn 600 mg			
	Gabapentin Concentration			
	N	Mean	Std	Median
0	101	1720.91	741.64	1720.00
1	3	1560.00	467.65	1830.00
2	1	1450.00	.	1450.00
All	105	1713.73	731.08	1720.00

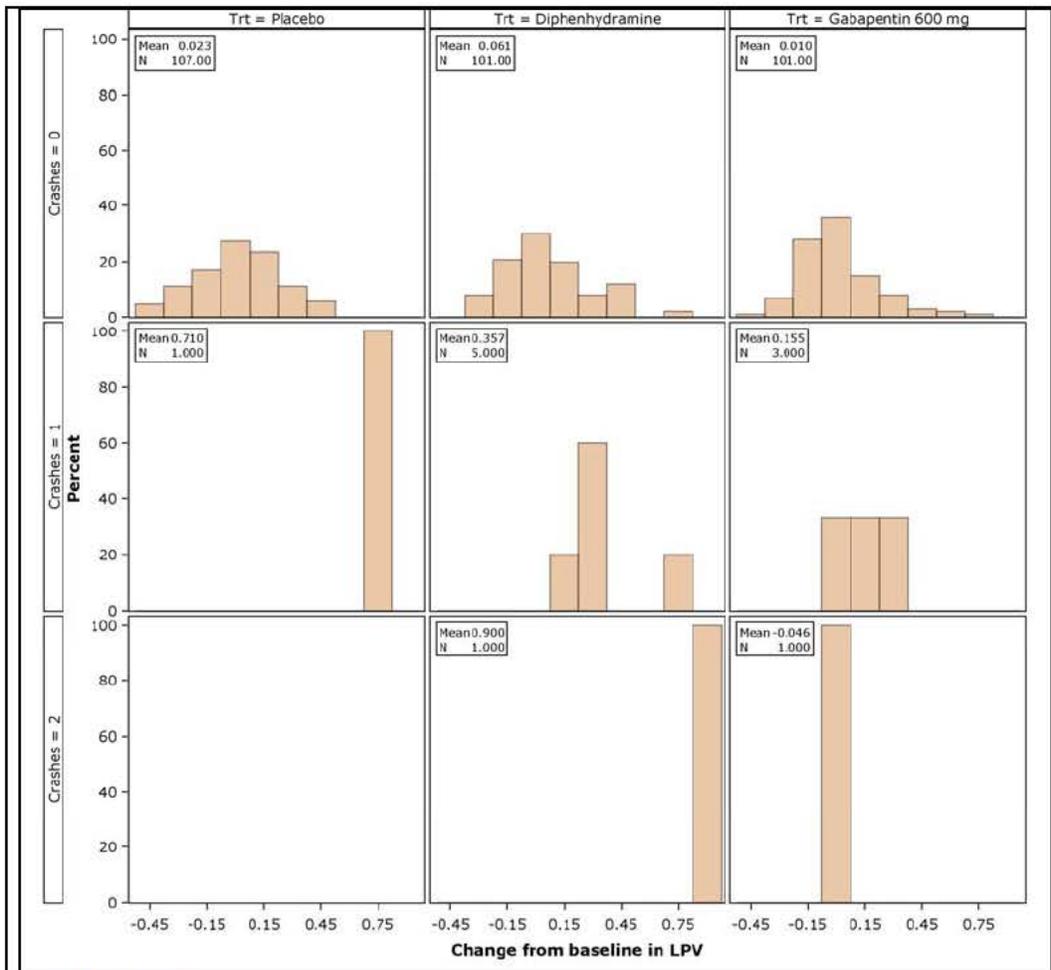
The data shows that there is no clear relationship between number of crashes and gabapentin concentrations in healthy subjects and patients.

**Relationship between lane position variability and number of crashes**

Figure below shows distribution of change from baseline in lane position variability in placebo, diphenhydramine and gabapentin treatment groups. The data obtained from RLS patients and healthy subjects are shown below.

**Gabapentin Plasma Concentration (ng/mL) Versus Baseline, Placebo Corrected Change in Lane Position Variability in RLS Patients and Healthy Subjects**





Healthy Subjects

The figure above suggests that, in RLS patients, the number of crashes at gabapentin doses of 1200 and 1800 mg are higher when compared to diphenhydramine. The study in healthy subjects, at a dose of 600 mg, also showed greater number of crashes when compared to placebo.

Conclusion	<ul style="list-style-type: none"> <li>• The effects of 600 mg gabapentin dose on lane position variability are lesser when compared to diphenhydramine.</li> <li>• The number of crashes are higher for 600 mg group in comparison to placebo. Based on cross study comparison, it appears that the number of crashes are lower for 600 mg group when compared to 1200 and 1800 mg groups.</li> </ul>
------------	--

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

/s/  
-----

-----  
VENEETA TANDON  
10/15/2012

VENKATESH A BHATTARAM  
10/15/2012

TA-CHEN WU  
10/18/2012

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022399Orig1s005**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022399

SUPPL # 005

HFD # 120

Trade Name Horizant

Generic Name gabapentin enacarbil extended-release tablets

Applicant Name Xenoport

Approval Date, If Known

### 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

SE8

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.

N/A

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:

This prior approval supplement provides safety labeling changes based on two Post-Marketing Requirement studies: a simulated driving study (Protocol RXP114111) with 600 mg/day gabapentin enacarbil (PMR# 1588-7) and a morphine drug interaction study (Protocol RXP115720) (PMR# 1588-10).

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

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:
- Simulated driving study (Protocol RXP114111) with 600 mg/day gabapentin enacarbil (PMR# 1588-7)
  - Morphine drug interaction study (Protocol RXP115720) (PMR# 1588-10)

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

Investigation #2 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

Investigation #2 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"):

- Study RXP114111: A randomized, double-blind, active and placebo-controlled, crossover study assessing the effect of 600 mg Gabapentin enacarbil (GEn) on simulated driving in healthy subjects
- Study RXP115720: A double-blind, 3-part crossover study to assess the pharmacokinetics and tolerability of single doses of gabapentin enacarbil and morphine

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 # 071352 YES  ! NO   
! Explain:

Investigation #2 !

IND # 071352      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: Nicole L. Bradley, PharmD  
Title: Regulatory Project Manager, Division of Neurology Products

Date: March 6, 2013

Name of Office/Division Director signing form: Russell G. Katz, MD  
Title: Director, Division of Neurology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/  
-----

NICOLE L BRADLEY  
03/06/2013

RUSSELL G KATZ  
03/06/2013

## Bradley, Nicole

---

**From:** Bradley, Nicole  
**Sent:** Tuesday, February 05, 2013 5:43 PM  
**To:** Greg Bates  
**Cc:** Bradley, Nicole  
**Subject:** NDA 022399/S-005 Horizant: Information Request\_February 5, 2013

Hi Greg,

Reference is made to NDA 022399/S-005. We have the following questions and requests:

What is recorded by the software program, if the subject vehicle edge crosses the center dividing line to a distance that would meet the perimeter of an oncoming vehicle but there is no oncoming at the time of the lane crossing (only 1 auto pass in the opposing lane every 10 minutes)? If lane crossing is not recorded as a crash please recalculate the data to record "potential crashes" as anytime the subject's vehicle edge crosses the center divider or right edge (beyond + 13 ft. or -13 ft.). Evaluate the entire test time not just the 1 minute window surrounding a crash. Provide the total number of potential crashes, mean, median, outlier analysis for each treatment group for each test time. Provide the information for the baseline and change from baseline for each parameter as well. Construct a model that includes the baseline number of simulated crashes and compare the results for each treatment group for each test time. If this is not feasible please explain why.

Please provide your response within 5 days.

I'd also like to confirm that we have received the briefing package material through the gateway for the March 5, 2013, meeting.

Thank you,  
Nicole

**Nicole L. Bradley, PharmD**  
Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
Food and Drug Administration

Office: 301-796-1930  
Fax: 301-796-9842  
Email: [nicole.bradley@fda.hhs.gov](mailto:nicole.bradley@fda.hhs.gov)

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

/s/  
-----

NICOLE L BRADLEY  
02/05/2013

**From:** [Bradley, Nicole](#)  
**To:** [Greg Bates](#)  
**Cc:** "[Debra.H.Lake@gsk.com](mailto:Debra.H.Lake@gsk.com)"; [Bradley, Nicole](#)  
**Subject:** NDA 22399/S-005: Response and Information Request\_January 7, 2013  
**Date:** Monday, January 07, 2013 11:51:41 AM  
**Attachments:** [LATLNPOS.xpt](#)

---

Hi Greg,

Reference is made to NDA 22399/S-005 and to your December 14, 2012, request for the RXP114111 analysis data which was referenced during the November 29, 2012, teleconference. Please find attached below the requested data.

Additionally, we have the the following requests for information:

1. Provide the following:

- o Overall road width
- o Width of each lane from median to edge of the road
- o Width of the median
- o Vehicles lane position (LATLNPOS variable from dataset) when a crash has occurred (minimum distance from center reference). Note: there are values for LATLNPOS that are greater than the value at the time of crash, yet there is no crash recorded.

2. Re-evaluate crash data to show potential crashes as instances when center of vehicle crosses the median (into left lane, potential oncoming traffic) or right edge line of right (travel) lane. We are seeing potential crashes that do not meet the criteria of >18 ft. past the median or right lane edge that would result in potential crashes according to other experts who look at simulated crash data.

3. Provide your interpretation of the re-analysis of the potential crash data that is being provided in the document attached above.

Please provide your response by February 1, 2013.

Thank you,  
Nicole

**Nicole L. Bradley, PharmD**

Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
Food and Drug Administration

Office: 301-796-1930

Fax: 301-796-9842

Email: [nicole.bradley@fda.hhs.gov](mailto:nicole.bradley@fda.hhs.gov)

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

/s/  
-----

NICOLE L BRADLEY  
01/07/2013



NDA 022399/S-005

**REVIEW EXTENSION –  
EFFICACY SUPPLEMENT**

GlaxoSmithKline  
Attention: Debra H. Lake, MS  
Director, Regulatory Affairs  
PO Box 13398, Five Moore Drive  
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your February 29, 2012, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Horizant (gabapentin enacarbil) extended-release tablets.

On November 9, 2012, we received your November 9, 2012, unsolicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 29, 2013.

If you have questions, call Nicole L. Bradley, PharmD, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

*{See appended electronic signature page}*

Russell G. Katz, MD  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

/s/  
-----

RUSSELL G KATZ  
12/21/2012

## Bradley, Nicole

---

**From:** Bradley, Nicole  
**Sent:** Friday, December 14, 2012 3:35 PM  
**To:** Greg Bates  
**Cc:** 'Debra.H.Lake@gsk.com'; Bradley, Nicole  
**Subject:** NDA 22399/S-005 Information Request\_December 14, 2012

Hi Greg,

Reference is made to NDA 022399/S-005. Please provide the following:

1. The make and model of the driving simulator used for studies XP083, XP088 and RXP114111. This should include both hardware and software.
2. The physical environment in which simulated driving assessments were performed for studies XP083, XP088 and RXP114111. The information should include physical location, conditions during assessment, instructions given to the subject as well as how assessments were monitored.

Please provide your response within 1 week.

Thank you,  
Nicole

**Nicole L. Bradley, PharmD**  
Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
Food and Drug Administration

Office: 301-796-1930  
Fax: 301-796-9842  
Email: [nicole.bradley@fda.hhs.gov](mailto:nicole.bradley@fda.hhs.gov)

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

/s/  
-----

NICOLE L BRADLEY  
12/14/2012

## Bradley, Nicole

---

**From:** Bradley, Nicole  
**Sent:** Tuesday, November 27, 2012 11:09 AM  
**To:** Debra Lake  
**Cc:** Bradley, Nicole  
**Subject:** NDA 022399/S-005 - PMR and milestone dates

Hi Debra,

Reference is made to NDA 022399/S-005 and to your correspondence dated November 9, 2012.

As discussed during our October 31, 2012, teleconference,

(b) (4)

(b) (4)

(b) (4)

We request your response within 1 week. Kindly provide your response by e-mail and follow with an identical archival submission.

Thank you,  
Nicole

**Nicole L. Bradley, PharmD**  
Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
Food and Drug Administration

Office: 301-796-1930

Fax: 301-796-9842

Email: [nicole.bradley@fda.hhs.gov](mailto:nicole.bradley@fda.hhs.gov)

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

/s/  
-----

NICOLE L BRADLEY  
11/27/2012

## Bradley, Nicole

---

**From:** Bradley, Nicole  
**Sent:** Wednesday, November 21, 2012 12:09 PM  
**To:** Debra Lake  
**Cc:** Greg Bates; Bradley, Nicole  
**Subject:** NDA 22399/S-005,006,007: FDA proposed label and rationale

**Attachments:** FDA\_ProposedChanges\_NDA 022399\_S567\_2012\_1121.doc

Dear Debra,

Reference is made to NDA 022399 and to Supplement 5 (submitted on February 29, 2012), Supplement 6 (submitted on March 20, 2012), and Supplement 7 (submitted on April 25, 2012). Reference is also made to your June 22, 2012, submission, which included a draft package insert incorporating your proposed revisions for all three supplements. Attached please find our proposed labeling revisions in tracked changes. Please note, we used your June 22, 2012, proposed label (accepting all tracked changes), as our base document. Additionally, our rationale for our proposed changes related specifically to Supplement 5, is provided below.



FDA\_ProposedChanges\_NDA 022399...

To this end, we would like to schedule a teleconference with you and your team for Thursday, November 29, 2012, between 4:00 and 4:30 PM EST to discuss the proposed label and proposed Post-Marketing Requirement (PMR). Please confirm your availability.

### **Rationale for Supplement 5 Labeling Revisions**

The proposed changes to Section 5.1 (Warnings and Precautions) describe the results and trial population of study RXP114111. We do not agree with the conclusion that the increased number of crashes reported in the mid-day test period for subjects who received diphenhydramine and Horizant are due solely to chance. Although an increase in lane Position Variability (LPV) was not observed during the mid-day time point, an increase in LPV may be more closely related to peak blood concentration for diphenhydramine and Horizant. Increased Speed Variation (SV) was observed in individual patients who had simulated crashes and mean SV was increased at time points when crashes were reported. Although we acknowledge that the crashes seen at mid-day for both the control and Horizant groups did not correspond to Tmax for either drug, this does not, in our view, undermine the empirical findings. In this regard, it is worth noting that the number of crashes seen at mid-day in both treated groups was the same as was seen at Tmax for DPH, a finding you acknowledge is likely drug related (presumably because it occurred at Tmax). The same number of crashes seen at mid-day for both drugs raises our concerns that they, too, are drug related, despite the timing of their occurrence.

Regarding the question of the comparability of the RLS and healthy volunteer populations, we note that the Division discussed our priorities for information from study RXP114111 during the May 24, 2011, teleconference with representatives from your firm. The first priority was to determine the duration of driving impairments associated with Horizant. You argued for a study that could be turned around quickly to obtain information concerning the effect of 600 mg of Horizant on driving. You proposed testing in healthy volunteers to facilitate enrollment and completion of the study. The Division did not object to enrolling non-RLS, healthy subjects, but there is no record that we concluded, nor did we conclude, that there was no difference between patients with RLS and healthy subjects with respect to simulated driving performance. We also voiced our concern that the design of study RXP11411 would not provide information about the duration of driving

impairments in patients starting treatment with Horizant.

With respect to any differences in driving performance between patients with RLS and healthy volunteers, an association of increased SV and simulated crashes in patients with RLS compared to control subjects was noted in the XP088 study report. More subjects with RLS (n=2) crashed during the Day 2 morning simulated driving evaluation) compared to the previous day's driving evaluation at 4 PM (n=0) in XP088. The final report for study XP088 described increased crashes and SV occurred in selected patients with RLS. Your own report of this study includes the following statement,

“The worsening of driving performance in the later epochs of the test observed in these RLS individuals is typically seen in subjects with sleep disorders or sleep deprivation [Risser, 2000; Ware, 2006; May, 2005] and suggests that sleep disturbance caused by RLS may affect driving performance in selected subjects whose psychomotor function may be more prone to sleep deprivation.” Therefore, there is reason to believe that patients with RLS may have a different degree of driving impairment than healthy volunteers.

Thanks,  
Nicole

**Nicole L. Bradley, PharmD**  
Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
Food and Drug Administration

Office: 301-796-1930  
Fax: 301-796-9842  
Email: [nicole.bradley@fda.hhs.gov](mailto:nicole.bradley@fda.hhs.gov)

28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page

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

/s/  
-----

NICOLE L BRADLEY  
11/21/2012

## Bradley, Nicole

---

**From:** Bradley, Nicole  
**Sent:** Friday, June 29, 2012 1:39 PM  
**To:** 'Debra Lake'  
**Cc:** Bradley, Nicole; 'eric.b.benson@gsk.com'  
**Subject:** Horizant NDA 22399 S-005: Information Request\_June 29, 2012

Hello Debra and Eric,

Reference is made to NDA 22399 and to Supplement 005 submitted on February 29, 2012. We have the following information request:

Please provide additional analyses of the trials data for RXP114111. We are interested in the relationship (correlation) between level of alertness and a potential effect on driving. The analyses should match the relationship between change in the somnolence visual analog score (VAS) pre- versus post-driving assessment, lane position variability (LPV), speed variability (SV) and crashes by the driving assessment timepoint (evening, morning, midday) and treatment group (placebo, GEn, diphenhydramine), without regard to sequence. We noted that crashes were categorized in two ways:

1. Crash into another vehicle (categorized as 1)
2. Went off road and crashed (categorized as 2)

The computational method used to calculate the number of crashes, as noted in the define file for STISIM.CRASH, is a count of the number of times STISDTL.CRASHC changes. We request clarification on the count of crashes, and would like the data presented with total number of crashes (any type) by treatment and timepoint.

In addition, you have defined the variable VASCHB, as VAS change from baseline (VASCHB=VASCR-VASBASE). Please clarify whether VASBASE refers to VAS score recorded at Day -1/1 or pre-simulated driving test Day 5/6.

Change in VAS should be calculated as pre-simulated driving VAS score minus the post-simulated driving VAS score, for each timepoint. The total number of crashes should include all crashes regardless of the type of crash.

Timepoint	Treatment (N)	LPV (Mean, SD)	SV (Mean, SD)	Change in VAS (Mean, SD)	Crashes (number)	Plasma gabapentin concentration
Day 5 PM						
	PBO					
	GEn					
	DPH					
Day 6 AM						
	PBO					
	GEn					
	DPH					
Day 6 Midday						
	PBO					
	GEn					
	DPH					

Please provide your response to this request as soon as possible, but no later than July 6, 2012.

Thanks  
Nicole

**Nicole L. Bradley, PharmD**  
Regulatory Project Manager

Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
Food and Drug Administration

Office: 301-796-1930

Fax: 301-796-9842

Email: [nicole.bradley@fda.hhs.gov](mailto:nicole.bradley@fda.hhs.gov)

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

/s/  
-----

NICOLE L BRADLEY  
06/29/2012

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW  
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO:  <b>CDER-DDMAC-RPM</b> <b>Attn: Quynh-Van Tran and Sharon Watson</b>	FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Nicole Bradley, PharmD</b> <b>Regulatory Project Manager</b> <b>Division of Neurology Products</b>
---	--

REQUEST DATE June 18, 2012	IND NO.	NDA/BLA NO. 22399/S-005	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)  Labeling supplement w/clinical data
-------------------------------	---------	----------------------------	--

NAME OF DRUG Horizant (gabapentin enacarbil)	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Restless Leg Syndrome	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) September 24, 2012
---	------------------------------------	---	--

NAME OF FIRM: GSK	PDUFA Date: December 29, 2012 (Plan to act on this supplement October 18, 2012)
----------------------	---

**TYPE OF LABEL TO REVIEW**

<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION
--	---	---

**EDR link to submission:**

The entire submission can be found at the following link: <\\Cdsub1\evsprod\NDA022399\0093>

Labeling Link: <\\Cdsub1\evsprod\NDA022399\0093\m1\us\114-labeling\1141-draft>

**Please Note:** There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

**COMMENTS/SPECIAL INSTRUCTIONS:**  
Please note: we plan to include pending labeling supplements s-006 and s-007 in our action for Supplement 005 (Driving study)

**S-005: Prior Approval Labeling Supplement w/ Clinical Data:** Submission details

- Results of the 2 PMR studies provided in this submission are the basis for modifying the approved label
- Proposed labeling revisions include:
  - Section 5.1 Warnings and Precautions - Effects on Driving
  - Section 12.3 Clinical Pharmacology - Pharmacokinetics
  - Section 17.1 Patient Counseling Information - Effects on driving

Labeling Link: <\\Cdsub1\evsprod\NDA022399\0093\m1\us\114-labeling\1141-draft>

**PMR Final Study Reports Submitted in support of labeling change**

- PMR 1588-7 - simulated driving study with 600 mg/day Horizant (Protocol RXP114111)  
<\\Cdsub1\evsprod\NDA022399\0093\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\primary-rls\5354-other-stud->

[rep\rxp114111](#)

- PMR 1588-10 - drug-drug interaction study with morphine (Protocol RXP115720)

[\\Cdsub1\evsprod\NDA022399\0093\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\rxp115720](#)

**Review Timeline and Upcoming Meetings**

July 3: Team meeting

August 2: Team Meeting

September 21: Reviews to be completed

September 24: Labeling meeting

- Revisions to label should be in made in the e-room prior to meeting

- Send label to sponsor

October 3: Labeling meeting (tcon with sponsor)

October 10: Labeling meeting (possible tcon with sponsor)

October 15: **\*\*if needed\*\*** Labeling meeting

**October 18: Planned Action date**

SIGNATURE OF REQUESTER

Nicole L. Bradley, PharmD

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

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

/s/  
-----

NICOLE L BRADLEY  
06/18/2012



NDA 022399/S-005

**ACKNOWLEDGEMENT --  
PRIOR APPROVAL SUPPLEMENT**

GlaxoSmithKline  
Attention: Debra H. Lake, M.S.  
Director, Neurosciences, Global Regulatory Affairs  
PO Box 13398, Five Moore Drive  
Research Triangle Park, NC 27709

Dear Ms. Lake:

We have received your 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:** 005  
**PRODUCT NAME:** Horizant (gabapentin enacarbil) Extended-Release Tablets  
**DATE OF SUBMISSION:** February 29, 2012  
**DATE OF RECEIPT:** February 29, 2012

This supplemental application proposes labeling revisions to the following sections: Warnings and Precautions, Clinical Pharmacology, and Patient Counseling Information.

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 April 29, 2012, 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 Neurology 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, please call me at (301) 796-1930.

Sincerely,

*{See appended electronic signature page}*

Nicole L. Bradley, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

/s/  
-----

NICOLE L BRADLEY  
03/09/2012