CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	04/05/2011
From	Gerald D. Podskalny, DO
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-399
Applicant	GlaxoSmithKline
Date of Submission	10/06/2011
PDUFA Goal Date	04/06/2011
Proprietary Name / Established (USAN) names	Horizant (gabapentin enacarbil)
Dosage forms / Strength	600 mg oral tablets
Proposed Indication(s)	1. moderate to severe symptoms of primary restless legs syndrome in adults
Recommended:	***Approval***

1. Introduction

Restless Legs Syndrome (RLS) is a common nervous system disorder with an estimated prevalence between 5 and 10% in the general population, with 2 to 3% experiencing symptoms severe enough to warrant treatment based on epidemiological studies in the US [Allen, 2003;Hening, 2004b].

The diagnosis of RLS is based on four clinical criteria developed by the International Restless Legs Syndrome (IRLS) Study Group:

- An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs;
- The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting;
- The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues;
- The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable, but must have been previously present.).

The net result of the symptoms of RLS is that patients with the disorder have difficulty falling asleep. Sleep can be disturbed further by periodic limb movements of sleep PLMS are estimated to affect more than 80% of all RLS patients.

Classification of RLS

RLS can be primary (idiopathic) or secondary to other conditions. Primary RLS is often associated with a family history of RLS. Secondary RLS has been associated with a variety of conditions and pathological disorders including iron deficiency, peripheral neuropathies, rheumatoid arthritis, Parkinson's disease, diabetes, and multiple sclerosis.

The mechanism of action of how gabapentin may improve the symptoms of RLS is unknown. Ropinirole (REQUIP®) and pramipexole dihydrochloride (Mirapex®) are non-ergot dopamine agonists and are the only agents currently approved by the Food and Drug Administration (FDA) for the treatment of moderate-to-severe primary RLS. (b) (4) There are published reports describing off label use of Gabapentin for the treatment of RLS and is included in RLS treatment guidelines. There is limited dose-response and safety information concerning gabapentin for the treatment of RLS.

The severity of RLS symptoms is rated using the "International Restless Legs Syndrome Rating Scale (IRLS-Rating Scale)"-10 Item scale rated 0-4 for each item (40 = maximum -most severe) score.

Very severe=31-40 points
Severe=21-30 points
Moderate=11-20 points
Mild=1-10 points
None=0 points

2. Background

The NDA was initially submitted to the FDA on January 9, 2009 as a 505(b)(1) NDA by GlaxoSmithKline (GSK) and XenoPort. Upon completing the review (10 month plus a 3 month extension) on February 9, 2009, the agency issued a Complete Response (CR) action letter. The CR action was based primarily on concerns described in the results of the 2-year carcinogenicity study performed in Wistar rats demonstrating an increased incidence of pancreatic acinar carcinoma and adenoma. The finding of an increased risk for pancreatic acinar cell carcinoma in the GE carcinogenicity study replicated a similar finding of pancreatic acinar carcinoma reported in the gabapentin (Neurontin) 2-year carcinogenicity study. The concern regarding the finding of pancreatic acinar carcinoma for Horizant was greater because:

- The signal for pancreatic acinar carcinoma was seen in more animals and a lower dosages in the GE 2-year carcinogenicity study compared to the finding in the gabapentin study.
- The finding in the GE carcinogenicity study independently replicated the findings reported in the gabapentin carcinogenicity study

At the End of Phase II meeting, the sponsor asked members of the FDA review staff
If they would view a positive finding in the carcinogenicity, study would be an approvability issue (see beow).

Excerpts from the December 6, 2005, End of Phase II Meeting between XenoPort and FDA

XenoPort Question #4

4. Assuming that there is a finding of pancreatic acinar cell tumors in rats from XP13512 exposure, does the Agency agree that, like gabapentin, this specific finding is not an issue for approval of XP13512?

FDA Response
The significance placed on any animal tumor findings will depend on the strength of the signal compared to that seen with gabapentin taking into account the new indication and the efficacy demonstrated clinically.

The sponsor concluded the results of the 2 year carcinogenicity study for Horizant indicated there was an increased incidence of pancreatic acinar cell tumors (adenomas and carcinomas) in both sexes at 5000 mg/kg/day with more males affected than females. Pancreatic acinar cell tumors also appeared to be slightly increased in males at 2000 mg/kg/day.

The sponsor also concluded the relevance of the animal signal to the human risk for carcinoma remained unclear but they believed it was similar to the risk associated with approved gabapentin. The sponsor's original NDA submission did not contain data that adequately supported the company's position that the signal for pancreatic acinar carcinoma reported in the carcinogenicity study was not relevant to humans. Furthermore, the company did not justify the risk in terms of the lower morbidity and absence of mortality associated with RLS compared to patients with refractory epilepsy. There is no mortality caused as a direct result of RLS compared to patients with refractory epilepsy. Epilepsy patients have an increased risk for sudden unexplained death (SUDEP) not present in patients with RLS. The CDC annual statistic for deaths in the U.S., listed 949 individuals died with epilepsy listed as cause of death compared to no fatalities associated with RLS. Furthermore, the potential for loss of occupation and economic loss is also greater for patients with epilepsy compared to RLS.

3. CMC/Device

Summary of CMC Initial Review
There was no new CMC data included in the company's Complete Response resubmission. Lists of the key CMC issues from the first cycle review are summarized.

The CMC review team recommended for **APPROVAL** for NDA 22-399, Horizant (gabapentin enacarbil) ER Tablets**.**

Expiry
GE was granted a 36 month expiry for the 600 mg tablet strength based on storage at room temperature, 25° C (77° F); with excursions permitted to 15 to 30° C (59 to 86° F). The stability of the drug product was found to be adequate. Initially the dissolution specifications were felt to

be overly discriminating but this was eventually resolved during a teleconference with the sponsor.

Environmental Impact Assessment
There were no significant findings (FONSI) from the Environmental Impact Assessment.

Facilities Inspection
The facilities inspection were all acceptable. The applicant provided comparability protocol for the post approval site changes for drug substance manufacture, release testing, and stability testing with the proposed data package that will be submitted in the Annual Report. However, FDA inspection of the proposed site is needed in addition to the proposed data package, which needs to be submitted in a CBE-30 supplement.

Review Issues-Resolved
The sponsor's proposed (b) (4)

4. Nonclinical Pharmacology/Toxicology

The Pharmacology Toxicology review of the 2-year carcinogenicity study for GE was a key component in the FDA's decision to issue a Complete Response action. There was replication of the signal for an increased risk for pancreatic carcinoma reported in the Neurontin carcinogenicity study. In the case of GE, pancreatic adenoma and acinar carcinoma were found in more animals, at lower doses and the tumors had signs of being more locally invasive compared to findings for Neurontin. The NDA did not include additional data from mechanistic studies in animals or pharmacoepidemiological studies supporting the company's position that the animal findings were not relevant to humans treated chronically with GE. Furthermore, the original NDA submission did not justify the potential risk of carcinoma and potential benefit of GE in light of the absence mortality and reduced morbidity associated with RLS compared to patients with refractory epilepsy.

From The FDA's Complete Response Letter

> *"The no effect doses for carcinoma were 500 and 2000 mg/kg/d in male and female rats, respectively, corresponding to exposures of approximately 8 times and 28 times the exposure in humans at a daily dose of 600 mg. Moreover, in a model where frank carcinoma has been observed, acinar cell hyperplasia and adenoma can be viewed as pre-cancerous lesions; there were trends for dose-related increases in these lesions in both*

sexes. Although the numbers are small, there appear to be excess adenomas in male rats at the lowest dose tested (500 mg/kg/d), such that the no-effect dose has not been established.

The non-clinical findings from the gabapentin enacarbil application substantiate the findings from the prior gabapentin NDA: there is now unequivocal evidence that gabapentin (and its pro-drug, gabapentin enacarbil) cause dose-related pancreatic acinar cell carcinoma in rats. One of the difficulties in extrapolating this risk to humans is the rarity of this particular tumor type: the vast majority of human pancreatic cancers are ductal in origin; acinar tumors are rare".

At the End of Review Meeting, GSK asked if they could convert the NDA for GE from a 505(b)(1) application to a 505 (b)(2) application to rely on information in the gabapentin label and published reports describing the gabapentin (Neurontin) carcinogenicity study results. After consultation with several offices, the agency determined GSK could resubmit the GE as a 505(b)(2) NDA.

The FDA Interpretation of the DE Carcinogenicity Study Results

The results of a 104-week oral (dietary) carcinogenicity study of to support the NDA for Neurontin (gabapentin) was conducted in rats at doses of 250, 1000, and 2000 mg/kg/day. The results were published by Sigler *et al*. (Sigler RE *et al. Toxicology* 98:73-82, 1995)

The review of the study findings and a summary table of the microscopic findings in pancreatic acinar cells of males were presented in Dr. Freed's original review.

FINDING	DOSE (mg/kg)			
	0	250	1000	2000
hyperplasia	21/50	22/50	20/50	23/50
adenoma	7/50	6/50	10/50	16/50
carcinoma	0/50	4/50	3/50	8/50

<u>Combined Pancreatic Lesions in Rats Treated with XP13512 for Up to 104 Weeks</u> (FDA Pharm-Tox Review, Dr. Freed)

FINDING	MALES				FEMALES			
	0	500	2000	5000	0	500	2000	5000
NEOPLASTIC								
adenoma	2/60	4/60	4/60	8/60	0/60	0/60	0/60	3/60
carcinoma	0/60	0/60	1/60	1/60	0/60	0/60	0/60	1/60
total	**2/60**	**4/60**	**5/60**	**9/60**	**0/60**	**0/60**	**0/60**	**4/60**
NON-NEOPLASTIC								
hyperplasia								
minimal	8/60	2/60	4/60	5/60	1/60	0/60	2/60	5/60
mild	3/60	6/60	7/60	12/60	0/60	0/60	1/60	5/60
moderate	3/60	1/60	3/60	3/60	0/60	1/60	1/60	4/60
severe	0/60	1/60	0/60	0/60	0/60	0/60	0/60	0/60
total	**14/60**	**10/60**	**14/60**	**20/60**	**1/60**	**1/60**	**4/60**	**14/60**

FDA Pharmacology Toxicology supervisory review (Dr. Freed) referenced published data by Radulovic LL et al. Drugs Today 31(8):P597-611, 1995; Sigler RE et al., 1995 and labeling (Package Insert, 4/23/09) for gabapentin. The review noted several important differences between the carcinogenicity study finding for gabapentin (Neurontin) and GE (XP13512, aka Horizant).

- Pancreatic acinar cell adenomas and carcinomas were observed in both males and females with XP13512, whereas these tumors were observed only in males treated with gabapentin. [It is of note that the spontaneous incidence of pre-neoplastic and neoplastic changes in pancreatic acinar cells was lower in females than in males.]

- A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was observed in XP13512-treated males at the mid and high doses, but reported only at the high dose in males treated with gabapentin.

- The pancreatic acinar cell carcinomas detected in XP13512-treated males and females were described in the study pathologist's report as "locally invasive without evidence of distant metastases"; the acinar cell carcinoma was the cause of death in the affected mid-dose male, but not in the high-dose animals. The pancreatic acinar cell tumors reported for gabapentin were "…considered low grade since they did not invade adjacent tissues, metastasize or cause the death of any animal…" (Radulovic et al., 1995).

- The incidence of pancreatic acinar cell hyperplasia was dose-related in males and females treated with XP13512, whereas with gabapentin, the incidence of hyperplasia was similar among groups in males.

Dr. Freed reviewed published reports from several studies intended to investigate possible mechanisms responsible for increased incidence of pancreatic acinar carcinomas in rats given gabapentin. A series of studies by Dethloff et al (*Toxicol Sci* 55:52-59, 2000) were unable to confirm that an increase in CCK receptor expression was responsible for an increased sensitivity to CCK, in turn leading to an increase in pancreatic acinar carcinoma.

There were no tumor findings reported in a 104 week carcinogenicity study in mice for GE or for Neurontin.

Gabapentin Carcinogenicity Study Results From The Neurontin Label
Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day.

By comparison, the tumor findings in the Neurontin carcinogenicity study were in fewer animals, in a single sex (males) and at higher doses. Pancreatic carcinoma was reported in high dose animals only in males providing a larger difference between the level of exposure associated with the tumor effect in male rats and the exposure to gabapentin derived from GE in humans at the recommended dose for treatment of RLS.

The Sponsor's Attempt to Study The Mechanism Underlying the Increased Incidence of Pancreatic Acinar Carcinoma in Rats.

In the sponsor's resubmission, they reported the results of a pilot study (XP101 (EFF-R1769-13512) to determine if it was technically feasible to detect differences in CCK levels after a single dose of GE versus a vehicle control and an active control (casein), in male Wistar rats. The sponsor tested 2 commercially available assays for their ability to detect small changes in CCK levels, in two independent laboratories. The increase in CCK level in response to 5000 mg/kg of GE was only slightly greater than the elevation in CCK observed in the animals that received the vehicle control. Both labs reported similar results indicating that the difference between the CCK elevations observed for the vehicle control animals and the GE treated animals was too small to distinguish reliably using the currently available assays.

The Sponsor's Interpretation of the Carcinogenicity Data Provided in The Resubmission.

> "First, the threshold dose for a carcinogenic effect was 2000 mg/kg/day of gabapentin enacarbil [RD2008/00347/00]. At this dose, there was no clear increase in hyperplasia, no increase in adenomas, and only one carcinoma. Therefore, this dose was associated with the minimum possible carcinogenic response and must be considered close to the threshold of no-effect. The systemic exposure to gabapentin at this dose was AUC=1950 μg.h/mL, which is 38-fold higher than the systemic exposure achieved clinically at the proposed dose in humans of 600 mg dose of gabapentin enacarbil for moderate-to-severe RLS.
>
> Second, GSK has demonstrated that gabapentin is accumulated 5- to 10-fold more in rat pancreas compared to human pancreas [2010N105598_00; Balkenohl, 1993]. Concentrations in the target tissue are more relevant than plasma levels in determining the response of the tissue to a potential carcinogen [m1.11.2, Safety Information Amendment (Nonclinical), Appendix 2]. This difference in tissue exposure must be considered when comparing human and rat exposures for calculation of safety margins. Even using the dose of 500 mg/kg/day where no carcinomas were seen, the calculation of a safety margin must take into account both the fact that plasma exposure was 11-fold that of the proposed human dose and the fact that rat pancreas accumulates the drug more than human pancreas. This would result in a safety margin of at least 50-fold.
>
> Third, the gabapentin enacarbil safety margin is provided by published information on the rat carcinogenicity study of gabapentin, where the no effect dose was determined to be 1000 mg/kg/day [Sigler, 1995; Neurontin Prescribing Information, 2009]. It has been demonstrated that plasma exposure in rats in that study would have been at least 25-fold that provided by the proposed human dose of 600 mg for moderate-to-severe RLS.
>
> Based on these approaches the calculated safety margin for the proposed clinical dose of 600 mg gabapentin enacarbil is above that designated by ICH guidelines as a limit for human relevance. Therefore, the data indicate an insignificant cancer risk to humans from the clinical use of gabapentin enacarbil at the proposed dose of 600 mg for moderate-to-severe RLS."

The Toxicology Review Team's Interpretation of the Non-Clinical Data
The sponsor did not demonstrate that the signal for pancreatic carcinoma reported in the 2-year carcinogenicity study is not relevant to humans. The review team did not find the sponsor's presentation of published reports concerning a high concentration of high affinity gabapentin transporter (LAT1) on human pancreatic islet cells compared to rats that have high concentration of LAT1 receptors in acinar cells compelling. Likewise, the argument that rats given gabapentin have high levels of the drug in pancreatic tissue as the potential mechanism responsible for the increased susceptibility for developing acinar cell carcinoma is also not convincing. Mice also have high level of gabapentin in pancreatic tissue and there was no signal for increased pancreatic carcinoma in the carcinogenicity study performed in mice. The increased risk for pancreatic carcinoma reported in rats compared to mice is not explained by differences in pancreatic tissue concentration. However, the primary and secondary toxicology reviewers concluded, the no tumor effect level in the 2-year carcinogenicity in rats is at the mid-dose (1000 mg/kg/day). This provides a safety margin between the exposures associated with the "no tumor effect" level in the GE carcinogenicity studies and the exposures associated with the recommended human dose (600 mg/day) in patients treated for the symptoms of RLS of approximately 25 fold.

Relevance to Humans
The
AERS Data Mining Results

Table 1. Data mining (MGPS) results for the HLT Pancreatic neoplasms malignant (excl islet and carcinoid). AERS data is current as of 4/8/2010. *

Generic Name	PT	SOC	N	EB05	EB95	EBGM
Gabapentin	Pancreatic carcinoma	Neopl	5	0.321	1.29	0.675

* **PT=MedDRA Preferred Term, SOC = System Organ Class, N = Number of reports**

In the Complete Response submission, the GSK conducted a review of postmarketing data and they reported a similar EB05 score for pancreatic carcinoma.

Epidemiological Data
During a May 18, 2010 meeting the company and the FDA agreed that the sponsor should take a multifaceted approach to provide evidence, that supports the company's position that the pancreatic acinar carcinoma signal reported in the 2-year carcinogenicity study in rats in not relevant to humans. The approach should include a demonstration of a mechanism to support that supports the theory that the risk for pancreatic acinar carcinoma is species specific. The response should also provide evidence that humans with long-term exposure to gabapentin do not have an increased incidence of pancreatic carcinoma. Published data by Freeman, et al[1] reported a possible signal for an increased for renal carcinoma in patients contained the Kaiser health record who were treated with gabapentin. The data had significant limitations, including the lack of multiplicity adjustment for 17,328 comparisons and lack of control for several important potential confounders. GSK conducted 2 case-control studies using the General Practice Research Database (GPRD) health records database from the U.K. to try and detect an increased risk for any cancer, pancreatic carcinoma, and renal carcinoma in patients treated with gabapentin. The sponsor completed the pharmacoepidemiological studies and included the results in their resubmission.

FDA DEPI Reviewer Comments and Conclusions for Studies WEUSKOP4774 and WEUSRTP4931

WEUSKOP4774 Risk of pancreatic cancer and renal cancer in patients exposed to gabapentin in the United Kingdom General Practice Research Database

WEUSRTP4931 Risk of cancer in patients exposed to gabapentin in the United Kingdom General Practice Research Database

The Sponsor conducted two parallel nested-case control studies in GPRD to examine the associations between gabapentin exposure and a number of cancer outcomes. The first study specifically examined the association between gabapentin exposure and the incidence of pancreatic and renal cancers in all patients exposed to gabapentin between January 1, 1993 and December 31, 2008. The second study examined the association between gabapentin exposure and the incidence of pancreatic and renal cancers in addition to cancers at the following sites: A) all cancer, B) stomach, C) anus, anal canal, and anorectum, D) lung and bronchus, E) bones and joints, F) breast, G) penis, H) urinary bladder, and I) other nervous system. This study used the same study design, but excluded patients with any previous cancer diagnoses prior to their first gabapentin exposure. In both studies, cases were risk set matched with up to 10 controls for sex, age at cohort entry (within two years), calendar year of cohort entry (within one year), and general practice site. Crude and multivariate odd ratios were presented for a no lag and a two-year lagged analyses. Statistically significant associations between gabapentin exposure and pancreatic and renal cancer was seen in analyses of never versus ever use and in no use versus the first tertile of use. In addition, a statistically significant association was observed for anus, anal canal, and anorectum cancer in no use versus the first tertile of use.

Overall, these associations were considered weak and unlikely to be causal. First, the associations between gabapentin exposure and cancer risk were not dose-dependent. Statistically significant associations were only seen in the first tertile of exposure, instead of observing a positive correlation between increasing exposure levels and risk. However, these studies may be underpowered to detect associations at higher gabapentin exposure levels since, as previously stated, most patients had limited exposure to gabapentin. Second, the likelihood that brief exposure to gabapentin is carcinogenic is questionable. The duration of use first tertile spanned from 0 to 1.55 months and the number of prescriptions first tertile spanned from 1 to 2 prescriptions. As such, all associations were attenuated in two-year lagged analyses. Third, the short duration between first exposure to gabapentin and incidence of renal or pancreatic cancer also calls into question gabapentin's carcinogenicity, especially given the long asymptomatic period associated with pancreatic cancer. The median latency between first gabapentin exposure and incidence was 416 days for renal cancer and 573 days for pancreatic cancer. Finally, the statistically significant associations observed are likely an artifact of a protopathic bias. Review of cancer diagnoses, inferred indication for gabapentin use, and READ codes recorded close to the first gabapentin exposure revealed that many patients were prescribed gabapentin for the treatment of paraneoplastic syndromes, or had a READ code indicating clinical suspicion of cancer prior to first gabapentin exposure that was presumably confirmed after subsequent diagnostic testing. For these reasons, the Sponsor's primary contention that any statistically significant association is a result of protopathic bias seems plausible.

Overall, the studies were well conducted. The Sponsors used an appropriate study design which included clinically relevant covariates. Furthermore, outcome definitions were either based on previously validated definitions or were verified by an independent cancer expert at the UK National Cancer Research Institute. The major limitation of this study was the small number of patients who had chronic gabapentin exposure; a limitation of the available data rather than a study design flaw. For example, pancreatic cancers cases were exposed to gabapentin for an average of 6.1 months and controls for an average of 9.6 months before the index date. Overall, this is similar to gabapentin use patterns in the U.S. Although, these GPRD studies

cannot address the risk of pancreatic or renal cancer in patients with chronic gabapentin use; it can address the risk of pancreatic or renal cancer in exposures which are typically seen in current clinical practice.

Overall, the GPRD studies submitted by the Sponsor and an earlier study from Kaiser Permanente Northern California do not provide evidence of a causal association between gabapentin use and cancer, in particular pancreatic and renal cancers. The GPRD studies suggest that any association between limited gabapentin exposure and cancer is likely explained by protopathic bias. Therefore, these studies do not provide a justification to deny the Sponsor's gabapentin enacarbil NDA. However, due to the aforementioned short duration of gabapentin use seen in current clinical practice, these studies cannot comment on the potential carcinogenicity associated with chronic gabapentin enarcarbil use.

If gabapentin enacarbil is approved, DEPI does not recommend further evaluation of gabapentin enarcarbil's carcinogenicity by means of an observational post-marketing requirement. Additional retrospective case-control and cohort studies would likely not add substantially different information to the risk-benefit discussion. A prospective registry study would be hard to interpret given pancreatic cancer's long asymptomatic period. In order to attribute any cancer association to gabapentin, registry participants would need to undergo imaging studies and potential biopsies at baseline to identify any prevalent pancreatic and renal cancer cases. Recruitment for such an intensive study would likely be difficult and is likely unwarranted given the currently available carcinogenicity data. Additional epidemiologic studies can be discussed if new gabapentin enacarbil carcinogenicity data is generated in the future.

Recommendation

The case control study using the GPRD health records database examining the potential of an increased risk for an "all cancer" signal and separately for renal and pancreatic acinar carcinoma was limited by inadequate long-term exposure to gabapentin among patients in the database. The same limits affected the Friedman[1] study, which used the Kaiser database, which also resulted in protopathic bias. The protopathic bias in this case is the detection of a false increased risk for cancer that is only significant when patients exposed to gabapentin for a very short time (<2 months), just prior to a cancer diagnosis, perhaps for pain due to the undiagnosed cancer are included in the risk analysis. I agree with the conclusions of the agency's DEPI reviewer that the methods, database and analysis employed in the two studies were adequate and that there are too few patients in the GPRD database with long-term use (> 2years) to provide meaningful assessment of a gabapentin associated increased cancer risk in humans. However, the GPRD data indicated that the long-term use of gabapentin for any indication is relatively short-term.

The absence of an increased reporting to the AERS database, absence of published reports cases of carcinoma associated with gabapentin, the findings of the paper byFriedman[1] , and the sponsor submitted GPRD case control studies, support the notion that long-term treatment with gabapentin is uncommon. Although, the situation may not be the same, for patients treated with Horizant used to treat patients for RLS. It is possible to monitor for the long-term use of Horizant in RLS and if there is substantial long-term use in this population, it may provide a more suitable database to study in the future. At this time, I agree there is insufficient information to conclude there is an increased risk for carcinogenicity in patients receiving gabapentin given its relative short-term use and the limits this places on the epidemiological data.

5. Clinical Pharmacology/Biopharmaceutics

The issues discussed in this section were resolved during this review cycle and resulted in postmarketing requirement imposed on the sponsor. There was no new clinical pharmacology studies submitted in the sponsor's resubmission.

Metabolism:
Following absorption from the intestinal tract, XP13512 undergoes extensive first-pass hydrolysis by non-specific carboxylesterases to form gabapentin with no other significant metabolites of XP13512. Neither XP13512 nor gabapentin are substrates, inducers or inhibitors of the major isoforms of human cytochrome P450, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 [Report PK-2003-002]. However, the potential of XP13512 and gabapentin to act as a substrate or inhibitor of CYP2C8 or 2B6 was not evaluated. The studies to evaluate the potential of XP13512 and gabapentin to be inhibitor of CYP2C8 and 2B6 have been presented to the sponsor as postmarketing requirements during this review cycle.

Dose Dumping in Alcohol
An alcohol interaction study was performed only using 40% alcohol compared to a buffer solution. The dissolution of XP13512 was increased by 20-30% within the first 2 hours. The sponsor's method of testing for alcohol interaction was not consistent with the agency's guidance and the dissolution at lower concentration of alcohol is not known. The clinical pharmacology reviewer recommended the sponsor repeat the alcohol interaction study in accordance with the agency's guidance.

Potential Drug-Drug Interaction with Morphine
The "Precautions" section of the Neurontin product label, under the "Information for Patients and Drug Interactions-Morphine" headings contains information from a published report of a potential drug interaction between 600 mg gabapentin and morphine.

> **Information for Patients**
> "Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of Neurontin or morphine should be reduced appropriately (see Drug Interactions)."
>
> **Drug Interactions (DI)**
> **"Morphine:** A literature article reported that when a 60-mg controlled-release morphine capsule was administered 2 hours prior to a 600-mg Neurontin capsule (N=12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine (see PRECAUTIONS). Morphine pharmacokinetic parameter values were not affected by administration of Neurontin 2 hours after morphine. The magnitude of interaction at other doses is not known."

Because the potential exists for a similar drug interaction in patients taking Horizant and morphine, the agency has asked the sponsor (3/31/11 T-con with GSK) to conduct a drug-drug interaction study to evaluate the effect on PK and clinical adverse reactions (especially sedation)

caused by co-administration of Horizant and morphine. The mechanism underlying the DI may be that morphine may increase may increase the G.I. transit time allowing for greater absorption of gabapentin (given as Neurontin). However, the magnitude of the potential increase in gabapentin levels cause by administration of morphine in advance of Horizant is unknown.

Clinical Pharmacology's Recommendation for Phase IV requirements

1. In vitro study for evaluation of the potential of XP13512 and gabapentin to be an inhibitor of CYP2C8 and 2B6.

2. The sponsor must repeat the alcohol dose dumping study using their final dissolution method and evaluate different concentrations of alcohol up to 40% (0, 5, 10, 20, and 40%).

3. Development of a 300 mg dose to be administered to patients with moderate to severe renal impairment and patients on hemodialysis.

4. Conduct a drug interaction study to evaluate the potential effects of morphine on the PK parameters of Horizant and gabapentin derived from Horizant. The study should also assess potential differences in the adverse reactions caused by co-administration of both drugs compared administration of Horizant alone.

Thorough QTc Study

The sponsor submitted the results of their thorough QTc study, which was reviewed by the QTc IRT during the first cycle. The moxifloxacin response failed to meet the agency's criteria for assay sensitivity. The problem could not be overcome by further analysis of the existing data and a repeat Thorough QTc study was recommended. However, the largest upper bounds of the 2-sided 90% CI for the mean difference between XP13512 6000 mg and placebo, and between XP13512 1200 mg

IRT Findings and Recommendations Regarding QTc Study

This study is inconclusive.

The QTc IRT recommended that the sponsor conducts a repeat Thorough QT study to fulfill the requirements outlined in ICH E14 guidelines. This was also made a PMR that was presented to GSK.

CDTL Comments

I agree with the Clinical Pharmacology (CP) reviewer's analysis that the dose-response analysis supports the approval of the 600 mg/day dose as the recommended dose, which should be taken at 5 PM. The postmarketing requirements that the sponsor evaluate the potential for Horizant to act as an inhibitor of CYP2C8 and 2B6, repeat the alcohol dose dumping study and evaluate tablet dissolution in different concentrations of alcohol, develop a 300 mg tablet for dosing in patients with severe renal impairment and to conduct a repeat thorough QTc study with adequate assay

sensitivity, were all previously presented to the sponsor and agreed to near the end of the NDA review. Representatives of GSK verbally agreed to the new postmarketing requirement to evaluate the potential drug interaction between morphine and Horizant during the 3/31/11 T-con. There are no outstanding Clinical Pharmacology issues and the review teams are in agreement with the proposed agency action and postmarketing requirements.

6. Clinical/Statistical- Efficacy

There was no new efficacy data contained in the sponsor's resubmission.

7. Safety

At the conclusion of the first review cycle, the sponsor's long-term safety study (XP-055) was still ongoing. The sponsor submitted the final study report for XP-055 to the FDA approximately 4 weeks before the application action date. The number of patients exposed to a dose of GE in the 120-day safety update exceeded ICH guidelines for the number of patients exposed to ≥600mg/day of GE for 6 and 12 months. In the agency's Complete Response letter, the sponsor was asked to update the ISS to include data from the final study report of study XP-055 and for any ongoing or completed studies involving GE for indication besides RLS. The final update did not contain any new safety from controlled clinical trials in RLS and the only new safety information reported to the All RLS study grouping was from study XP-055. However, the sponsor completed additional studies of GE in patients with migraine headache, peripheral neuropathic pain and post-herpetic neuralgia. The Final Safety Update report contained safety data from trial RXP110908, the RLS Sleep Disturbance Study but the complete study report (including efficacy and polysomnography data) was not included in the in the original NDA or in this resubmission. The trial was a placebo-controlled, 2 period crossover design with two 4-week treatment periods, a up-titration (3 days) and down-titration phase (7 days) at the beginning and end of the study and a taper down, wash-out and up-titration period of 2-weeks between the 2 treatment periods. All totaled patients (n-127) were only on a stable 1200 mg/day dose of GE for 4-weeks either in treatment period 1 or 2. Patients were only on GE 600mg/day during the taper periods.

The evaluation of new adverse reactions across the 3 safety data submission dates for trial XP-055 will highlight better the change in relative proportion of adverse reactions which may be less obvious using the larger number of subjects contained ALL RLS data grouping.

Dr. Goldstein (primary medical reviewer), describes the change in the proportion of adverse events in terms of both the XP-055 and All RLS safety grouping in her review.

Clinical Trials Results Contained in the Final Study Update (GSK Table)

Table 9 FSU and Original NDA 022399 ISS Study Groupings for Phase II and Phase III RLS Studies

Study Grouping	Studies	ISS[1]	120-Day SU[2]	FSU[3]
12-Week Placebo-Controlled RLS Studies (Integrated)	XP052, XP053, XP081	✓	-	-
All Placebo-Controlled Phase II & Phase III RLS Studies (Integrated)	12-Week Placebo-Controlled RLS Studies (XP052, XP053, XP081) plus: XP083, XP045	✓	-	-
All RLS Studies (Integrated and Individual)	XP052, XP053, XP081, XP083, XP060, XP021, XP045, XP055[4]	✓	✓	✓
RLS Long-Term Integration (Integrated)	12-Week Placebo-Controlled RLS Studies (XP052, XP053, XP081) plus: XP083, XP055[4]	✓	✓	✓

1. NDA 022399 ISS data cut-off date: 06 December 2007 (XP055 was the only ongoing study in the Phase II and III RLS CDP).
2. 120-Day SU data cut-off date: 31 July 2008 (XP055 was the only ongoing study in the Phase II and III RLS CDP)
3. All studies in the Phase II and III RLS CDP were complete as of the FSU data cut-off date of 18 June 2010.
4. XP055 is the only study contributing new safety information to the study groupings for the All RLS Studies and RLS Long-Term Integration grouping in this FSU

Patient Exposure by Clinical Trial (GSK Table)

Table 22 Enumeration of Unique Subjects Exposed to Investigational Product

	Number of Subjects		
	Placebo	GEn	Blinded Treatment
Unique Exposures in Clinical Pharmacology Studies	**39[1]**	**382**	-
Individual Phase II and Phase III RLS CDP			
XP052	108	113	-
XP053	96	226	-
XP081	41	176	-
XP083	64[1]	65	-
XP060	98	326	-
XP045	33	62	-
XP021	36	36	-
XP055 (GEn naïve subjects only)[2]	-	197	-
Total Phase II and Phase III RLS CDP	**476[2]**	**1201**	-
Completed GSK-Sponsored Phase IIIb RLS-Associated Sleep Disturbance Study			
RXP110908 (Polysomnography)	132	127	
Completed Neuropathic Pain Studies (XenoPort-Sponsored)			
XP009 (PXN111044) (PHN)	54	47	-
Completed GSK-Sponsored Studies in Neuropathic Pain			
PXN110448 (DPN)	120	234	-
PXN110527 (PHN)	0	94	-
PXN110748 (PHN)	95	276	-
Completed GSK-Sponsored Study in Migraine Headache Prophylaxis			
MPX111381 (Migraine Headache Prophylaxis)	128	395	
Completed/Terminated Astellas -Sponsored Studies			
Astellas Study 8825-CL-0003 (CTR ID No. NCT00530530)	-	-	474[3]
Astellas Study 8825-CL-0005	-	-	NA[4]
Astellas Study 8825-CL-0007 (CTR ID No. NCT00508430)	-	-	199[3]
Total Exposures in Other Indications	**529**	**1173**	**673**
Total Unique Exposures	**1044**	**2756**	**673**

Data Source: Table 1.2, Table 2.4, Table 3.1, Table 4.1, Table 5.1, Table 6.2, Table 7.1 and individual clinical pharmacology CSRs
NA=not available
Data cut-off: 18 June 2010

1. Subjects may have received placebo only or placebo and another investigational product.
2. The 197 GEn naïve 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.
3. Number of subjects enrolled.
4. The number of subjects enrolled is unavailable.

Exposure by Dose and Duration

Table 31 Duration of Subject Exposures by Randomized (Parent Studies) and Modal Dose (for XP055) for Mutually Exclusive Time Intervals (Safety Population: All RLS Studies)

Duration of exposure in months (days)	FSU: 18 June 2010 Number (%) of Subjects				
	GEn 600 mg (n=191)	GEn 1200 mg (n=770)	GEn 1800 mg (n=218)	GEn 2400 mg (n=21)	GEn All Doses (N=1201)
<3 (<91 days)	85 (45)	214 (28)	62 (28)	13 (62)	375 (31)
3 to <6 (91-181 days)	44 (23)	143 (19)	18 (8)	8 (38)	213 (18)
6 to <9 (182-272 days)	10 (5)	177 (23)	12 (6)	0	199 (17)
9 to <12 (273-364 days)	15 (8)	18 (2)	10 (5)	0	43 (4)
≥12 (≥365 days)	37 (19)	218 (28)	116 (53)	0	371 (31)

Data Source: Table 1.16.
The maximum length of exposure is included for each subject (including on-treatment and taper).
Note: For subjects who entered Study XP055, their extent of exposure in the parent study and in the follow-up study is combined. Exposure may not be continuous. For Study XP060, duration of exposure from the single-blind and double-blind phases are combined.
One subject had a modal dose of 0 and is not included in the above table. This subject was randomized to placebo plus diphenhyramine in parent Study XP083 prior to Study XP055 where the subject missed treatment for 4 of the 8 days while enrolled in the open-label extension study.

Cumulative Exposure of RLS Patients

613 patients received a clinically relevant dose of Horizant (≥ 600 mg/day) for 6 months or more and 371 received a clinically relevant dose for 1 year. The exposure exceeds the ICH recommendations for patient exposure to a drug intended to treat a chronic disease.

After the 120-day safety update report, data from an additional 58 (7%) patients who completed 1-year of treatment with GE were included in the final safety update.. In general, the relatively small increase in the number of completed patients did not change the safety conclusion for GE.

Data From the Long-Term, Open-Label Safety Trial XP-055

Study XP-055 was an open label, long-term safety study in which patients were titrated to a targeted dose of 1200 mg/day per protocol. All patients (naïve and non-naïve) began the trial on a dose of 600 mg/day at 5 PM for 3 days then all patients were increase to 1200 mg/day, if tolerated. Patients could increase the dose further to 1800 mg/day, reduce their dose or briefly stop Horizant and restart it again at the same or lower dose. As expected the majority (52%) of patients completed the trial on a dose of 1200 mg/day. However, the most frequent dose reduction was from 1200 mg/day to 600 mg/day (n=128) with more than half (67%, n=86) because of adverse event (see the table below).

Patient Disposition

Patient Withdrawal from Study XP-055 (GSK Table)

Table 8 Summary of Subject Disposition (Study XP055)

	Number (%) of Subjects[a]		
	Naïve N=199	Non-naïve N=382	Total N=581
Safety Population[b]	197 (99.0)	376 (98.4)	573 (98.6)
Completed	126 (63.3)	260 (68.1)	386 (66.4)
Prematurely Withdrawn[c d]	71 (35.7)	116 (30.4)	187 (32.2)
Primary Reason for Withdrawal			
Adverse event[cd]	29 (14.6)	35 (9.2)	64 (11.0)
Subject withdrew consent	19 (9.5)	37 (9.7)	56 (9.6)
Lost to follow-up	15 (7.5)	25 (6.5)	40 (6.9)
Treatment failure	3 (1.5)	8 (2.1)	11 (1.9)
Protocol non-compliance	2 (1.0)	8 (2.1)	10 (1.7)
Investigator judgment	2 (1.0)	2 (0.5)	4 (0.7)
Termination of study or withdrawal of subject by sponsor	1 (0.5)	1 (0.3)	2 (0.3)

Data Source: DS Table 6.1

Note: The listed reasons for early termination were those with a non-zero count for at least 1 prior exposure category (naïve/non-naïve).

a. Percentages were recorded as a function of N=581 subjects enrolled from parent studies XP052, XP053, XP081, and XP083.
b. Safety Population: all subjects who were enrolled in the study and were reported to have taken at least 1 dose (or any portion of a dose) of study medication.
c. Includes both treatment-emergent and non-treatment emergent AEs leading to withdrawal. Non-treatment emergent AEs leading to withdrawal are events that started prior to Study XP055 that did not worsen, and resulted in withdrawal during Study XP055.
d. Five subjects discontinued due to an adverse event that began during the parent study. These adverse events are not regarded as treatment-emergent in XP055.

Almost 1/3 of the randomized patients withdrew prematurely from XP-055, which is higher than expected even for a long-term (1 year) trial. The withdrawal rate is also higher compared to other long term studies for medications submitted to the FDA for approval as a treatment for RLS (Requip CR-not approved, reported (b) (4) early withdrawals). In placebo controlled trials of patients treated for post herpetic neuralgia, the dose of GE was higher for the assigned treatment arms, ranging form 1200 mg/day to a maximum of 3600 mg/day. Approximately 30% of patients withdrew prematurely from the post-herpetic neuralgia trial (PXN110448) prematurely but in the same trial 25% of patients assigned to placebo also withdrew prematurely. In trial PXN110748 again the proportion of patients who withdrew prematurely was again about 21-30% but 33% of the patients assigned to placebo withdrew prematurely, which was greater than all of the GE treatment arms (1200 mg, 2400 mg/day) except the group treated with 3600 mg/day (38% withdrew). In trial XP-053 patients with RLS were randomized to receive placebo, GE 600 mg/day, and 1200 mg/day (total n=325), more patient from the placebo group withdrew prematurely (21%) compared to 10% and 13% for the 600 mg/day and 1200 mg/day GE treated groups respectively. In trial XP-053, the primary reason patients gave for withdrawing early from the placebo group was because they experienced lack of efficacy or they withdrew consent but the percentage of patients who withdrew because of an adverse event was similar in all 3 treatment groups, including the placebo group. It seems reasonable that the higher percentage of patients who withdrew early from the post-herpetic neuralgia trials compared to XP-053 was because they were titrated, per protocol, to a much higher maximum dose of GE in the post-herpetic neuralgia trials compared to the maximum dose in the controlled RLS trials.

Subject Withdrawal by Trial and Reason in The ALL RLS Dose Grouping (GSK Table)

Table 126 Summary by Study of Subjects with a Disposition of WC, LTFU or IJ (All Subjects: All RLS Studies)

Study[1]	Treatment	Number of Subjects[1]		
		WC	LTFU	IJ
XP052	PBO	3	0	1
	GEn 1200 mg	4	0	0
XP053	PBO	8	1	0
	GEn 600 mg	3	1	0
	GEn 1200 mg	4	0	0
XP081	PBO	6	0	0
	GEn 600 mg	5	2	0
	GEn 1200 mg	4	3	0
	GEn 1800 mg	1	2	1
	GEn 2400 mg	0	3	0
XP083	PBO or PBO/diphenhydramine	2	0	0
	GEn 1200 mg	1	0	0
	GEn 1800 mg	0	0	0
XP055	GEn Naïve	19	17	2
	GEn Non-Naive	38	30	2
	Total (all subjects combined)	57	47	4
XP060[2]	GEn 1200mg (SB Phase)	27	12	NA
	PBO (DB Phase)	2	1	NA
	GEn 1200mg (DB Phase)	4	2	NA
Total	GEn All Doses[3]	112	70	5
	All Subjects[4]	131	74	6

Data Source: Table 8.1, Table 8.8, Table 8.15
NA=not applicable (not a disposition reason in XP060)

1. No subjects had a disposition of WC, LTFU or IJ in XP021 or XP045.
2. The referenced data source for disposition of subjects in Study XP060 summarizes subjects who completed the SB Phase then withdrew during the DB Phase under both the SB and DB columns. Table 8.4 and Table 8.8 summarize subjects in the study phase from which they withdrew.
3. Consists of all subjects exposed to GEn in a parent study and either discontinued the parent study or completed, enrolled into XP055, and did not take GEn in XP055; all who took GEn in XP055; all who took GEn in XP060 SB phase; and all who took GEn in studies XP021 or XP045.
4. Total (all subjects) who discontinued regardless of whether they ever took a dose of investigational product.

WC= Withdrew Consent, LTFU=Lost to Follow-up, IJ=Investigator Judgment

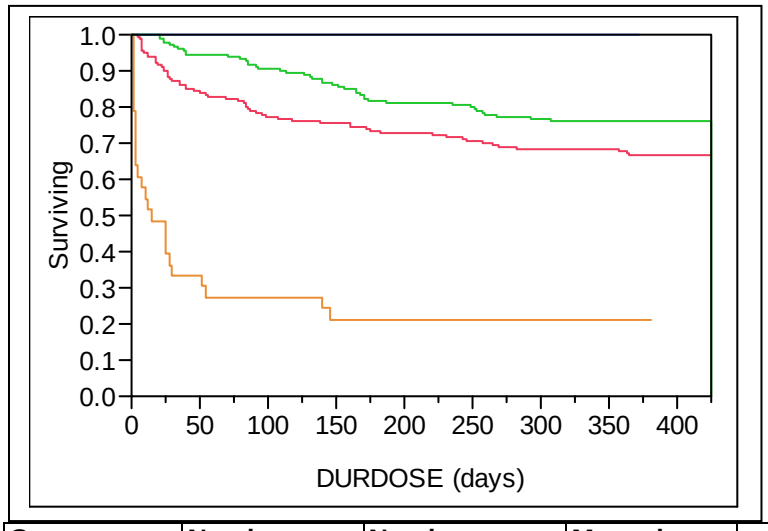
For all of the studies included in the NDA, the number of patients who withdrew prematurely from the All RLS trial grouping for reasons given as “Withdrew Consent”, “Lost to Follow-up”, “Terminated by the Sponsor and “Investigator Judgment” were unusually high.

The sponsor was asked for additional information regarding the patients who “withdrew consent” or were listed as “lost to follow-up”. GSK responded on 3/4/2011 with listings of any additional information (if available) for all of the patients who discontinued trial XP-055 early and As Dr. Goldstein reported in her review, many of these patients had also reported an adverse drug reaction however, the sponsor confirmed that all of the adverse events reported by these patients were captured in the adverse event tables and listings. Dr. Goldstein tallied the “primary reasons” given in the sponsor additional line listings as the reason for withdrawal. These were often transportation problems, job related scheduling conflicts or relocation but 24/57 patients were still listed as “unknown” or “no additional information.” These patients create doubt whether their withdrawal should be regarded as “missing completely at random” and perhaps they withdrew because of a reported adverse even or lack of effectiveness. In study XP-055, 195 patients withdrew early, of these only 65 withdrew at a final dose of 600 mg/day

Maximum Dose for Patients In Trial XP-055

Maximum Dose	N
0 mg or missing	8
600 mg	33
1200 mg	333
1800 mg	204
2400 mg	3

XP-055 Product-Limit Survival Fit



Survival Plot-% Patients Remaining in the Trial By Max Dose

1200 mg
1800 mg
2400 mg
600 mg

Summary

Group	Number withdrew early (days)	Number censored (completed)	Mean days in trial		Std Error
600 mg	26	7	49.0303	Biased	10.7234
1200 mg	110	222	365.264		10.9304
1800 mg	50	154	355.659		9.1851
2400 mg	0	3	.		.
Combined	186	386	343.637		19.2631

Quantiles

Group	Median Time to withdraw (days)	Lower95%	Upper95%	25% Failures	75% Failures
600 mg	15	3	29	3	140
1200 mg	499	.	.	160	499
1800 mg	425	.	.	425	425
2400 mg	.	.	.	.	.
Combined	425	425	.	165	499

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	109.4647	3	<.0001
Wilcoxon	130.4963	3	<.0001

The survival curves above with indicate the 600 mg treated group withdrew earlier and in higher percentage. All of the patients who entered XP-055 started on a dose of 600 mg/day. The large percentage of patients who withdrew very early in the 600 mg/day group were simply the patients who did not tolerate GE. Although about a third withdrew early in the 1200 mg (maximum dose) group, most occurred late in the trial suggesting they at least tolerated the 600 mg dose and the 1200 mg dose for a reasonable amount of time, even if you assume all patients who withdrew early did so because of an adverse event. There were too few patients that received the 2400 mg dose (n=3) to allow any conclusions about patients treated with this dose.

XP-055 Previous Treatment Assignment for Patients Who Withdrew Early

Treatment	n
DIPHENHYDRAMINE 50 mg	7
Placebo	66
XP13512 1200 mg	57
XP13512 1800 mg	17
XP13512 2400 mg	12
XP13512 600 mg	36

Just under 2/3 of all patients (n=109) who withdrew early received placebo, diphenhydramine 50 mg or GE 600 mg/day. Patients in study XP-055 were titrated to a targeted dose of 1200 mg/day therefore, 2/3 of the patients who withdrew were not previously exposed to a dose of GE 1200 mg/day or greater.

Prior Treatment of Patients Entering XP-055 Who Withdrew On a Maximum Dose=600 mg/day

Treatment	n
Placebo	12
XP13512 600 mg	2
XP13512 1200 mg	10
XP13512 1800 mg	1
XP13512 2400 mg	1

Number of Dose Reductions and Type in Trial XP-055 (GSK Table)

Table 21 Number of Dose Reductions by Reduction Type and Reason for Reduction (Safety Population: Study XP055)

Group Reason for Reduction	Number (%) of Subjects 1200 to 600 mg N=114	 1800 to 1200 mg N=52	 2400 to 1800 mg N=3
Naïve			
Number of Dose Reductions, n	56	15	1
Adverse Event	41 (73.2)	10 (66.7)	0
Per Protocol	3 (5.4)	0	0
Other	12 (21.4)	5 (33.3)	1 (100.0)
Non-Naïve			
Number of Dose Reductions, n	72	48	2
Missed Doses	1 (1.4)	0	0
Adverse Event	45 (62.5)	19 (39.6)	0
Per Protocol	4 (5.6)	0	0
Other	22 (30.6)	29 (60.4)	2 (100.0)
Total			
Number of Dose Reductions, n	128	63	3
Missed Doses	1 (0.8)	0	0
Adverse Event	86 (67.2)	29 (46.0)	0
Per Protocol	7 (5.5)	0	0
Other	34 (26.6)	34 (54.0)	3 (100.0)

Data Source: DS Table 8.3 and DS Listing 8

There were 199 subjects that decreased their daily dose of Horizant one or more times. The most common reasons for dose decreases were 'adverse event' and other. The dose was changed for 128 subjects that decreased their daily dose of Horizant from 1200 mg to 600 mg for 'adverse event' (86 [67.2%]) and 'other' (34 [26.6%]). 63 subjects that reduced their dose of Horizant from 1800 mg to 1200 mg, the most common reason for dose reductions were 'adverse event' (29 [46.0%]) and 'other' (34 [54.0%]).

A review of the sponsor's analysis datasets, found that most common specific reasons given for any dose change (up or down) that were classified as "other" described symptoms of loss of efficacy, which made up the majority of cases.

Withdrawal of Patients from Horizant in Trials for Other Indications.

Withdrawals from Trial PXN110748 in Patients with Painful Peripheral Neuropathy

Protocol: PXN110748 RXPFSU GEn (GSK1838262 / XP13512) Page 1 ‹
Population: Randomized

Table 5.2
Summary of Subject Disposition

	Placebo (N=95)	GEn 1200 (N=107)	GEn 2400 (N=84)	GEn 3600 (N=90)	Total (N=376)
Completion Status					
Completed	64 (67%)	85 (79%)	60 (71%)	56 (62%)	265 (70%)
Withdrawn	31 (33%)	22 (21%)	24 (29%)	34 (38%)	111 (30%)
Primary reason[1] for withdrawal					
Adverse event	12 (13%)	6 (6%)	12 (14%)	16 (18%)	46 (12%)
Lack of efficacy	6 (6%)	1 (<1%)	1 (1%)	4 (4%)	12 (3%)
Protocol deviation	5 (5%)	4 (4%)	4 (5%)	9 (10%)	22 (6%)
Study closed/terminated	0	0	0	0	0
Lost to follow-up	1 (1%)	2 (2%)	0	1 (1%)	4 (1%)
Investigator discretion	2 (2%)	2 (2%)	2 (2%)	0	6 (2%)
Withdrew consent	5 (5%)	7 (7%)	5 (6%)	4 (4%)	21 (6%)

Withdrawals from Trial MPX111381 for Prophylaxis of Migraine Headache

Protocol: MPX111381 RXPFSU GEn (GSK1838262 / XP13512) Page 1 of 1
Population: Randomized

Table 7.2
Summary of Subject Disposition

	Placebo (N=129)	GEn 1200mg (N=67)	GEn 1800mg (N=134)	GEn 2400mg (N=134)	GEn 3000mg (N=62)	Total (N=526)
Completion Status						
Completed	95 (74%)	49 (73%)	88 (66%)	97 (72%)	37 (60%)	366 (70%)
Withdrawn	34 (26%)	18 (27%)	46 (34%)	37 (28%)	25 (40%)	160 (30%)
Primary reason[1] for withdrawal						
Adverse event	11 (9%)	4 (6%)	17 (13%)	16 (12%)	13 (21%)	61 (12%)
Lack of efficacy	6 (5%)	1 (1%)	1 (<1%)	3 (2%)	1 (2%)	12 (2%)
Protocol deviation	6 (5%)	5 (7%)	4 (3%)	5 (4%)	3 (5%)	23 (4%)
Study closed/terminated	0	0	0	0	0	0
Lost to follow-up	3 (2%)	4 (6%)	5 (4%)	5 (4%)	3 (5%)	20 (4%)
Investigator discretion	0	0	5 (4%)	1 (<1%)	1 (2%)	7 (1%)
Withdrew consent	8 (6%)	4 (6%)	14 (10%)	7 (5%)	4 (6%)	37 (7%)

There was also a high percentage of patients who withdrew from clinical trials of Horizant for treatment of peripheral neuropathy and migraine. The percentage of withdrawals in each treatment are were similar to placebo except for patients treated with 3600 mg/day who were more likely to withdraw.

Adverse Drug Reactions (ADRs)

Deaths

There have been a total of 6 deaths during the entire GE clinical trials development program. Three deaths were reviewed in the first cycle review and there were three additional deaths reported in the final safety update. The 3 additional deaths, all of which occurred in patients receiving GE, were reviewed in detail by Dr. Goldstein. In the case of a patient enrolled in study MXP111481 for chronic migraine, the patient's death was listed as an "accidental overdose". Although, there was no suicide note left, it does not seem possible to know if the patient intended to end his life, therefore the patient's death should be considered a possible suicide. In the other two cases the deaths seem unrelated to treatment with GE.

Carcinoma

There were a total of six reports of carcinoma as of the June 18, 2010 data cut-off date. Of these subjects, five were treated with GE and one with placebo. One subject was eventually determined not to have a diagnosis of carcinoma. All events were considered by the investigator to be unrelated to investigational product with the exception of one subject in the Astellas sponsored study where the relationship between the diagnosis of lymphoma and treatment with GE was described as possible. A review of the narrative for this patient finds that a causal relationship between his exposure to GE (1200 mg/day for171 days) was unlikely.

Other Serious Non-Fatal Adverse Drug Reactions (ADR) All RLS Trial Group (GSK Table)

Table 84 Any TESAEs (Safety Population: RLS Long-Term Integration)

	Number (%) of Subjects					
	NDA Data Cut-off: 06 December 2007		120-Day SU Data Cut-off: 31 July 2008		FSU: 18 June 2010 Studies Complete	
Preferred Term	Total GEn (N=777)	Time since first dose (Days)	Total GEn (N=777)	Time since first dose (Days)	Total GEn (N=777)	Time since first dose (Days)
Any event	13 (2)	-	19 (2)	-	20 (3)	-
Back pain	0	-	2 (<1)	263 & 135	1 (<1)	135
Colitis	1 (<1)	8	1 (<1)	8	1 (<1)	8
Rotator cuff syndrome	1 (<1)	27	1 (<1)	27	1 (<1)	27
Intervertebral disc protrusion	1 (<1)	31	1 (<1)	31	1 (<1)	31
Cellulitis	1 (<1)	36	1 (<1)	36	1 (<1)	36
Meningitis viral	1 (<1)	38	1 (<1)	38	1 (<1)	38
Myocardial infarction	1 (<1)	41	1 (<1)	41	1 (<1)	41
Non-small cell lung cancer	1 (<1)	41	1 (<1)	41	1 (<1)	41
Angina unstable	1 (<1)	84	1 (<1)	84	1 (<1)	84
Cholecystitis acute	1 (<1)	111	1 (<1)	111	1 (<1)	111
Chest pain	1 (<1)	132	1 (<1)	132	1 (<1)	132
Lumbar spinal stenosis	1 (<1)	190	1 (<1)	190	1 (<1)	190
Pulmonary embolism	1 (<1)	263	1 (<1)	263	1 (<1)	263
Non-cardiac chest pain	1 (<1)	318	1 (<1)	320[2]	1 (<1)	320
Cerebrovascular accident	1 (<1)	321	1 (<1)	321	1 (<1)	321
Drug withdrawal syndrome	0	-	1 (<1)	147	1 (<1)	147
Appendicitis	0	-	1 (<1)	370	1 (<1)	370
Post procedural infection	0	-	1 (<1)	379	1 (<1)	379
Lumbar vertebral fracture	0	-	1 (<1)	263	1 (<1)	263
Road traffic accident	0	-	1 (<1)	182	1 (<1)	182
Transient ischemic attack	0	-	1 (<1)	235	1 (<1)	235
Mental status changes	0	-	1 (<1)	165	1 (<1)	165
Cholelithiasis	0	-	0	-	1 (<1)	56
Peripheral vascular disorder	0	-	0	-	1 (<1)	10
Herpes Zoster	0	-	0	-	1 (<1)	284
Exostosis	0	-	0	-	1 (<1)	168
Nerve root compression	0	-	0	-	1 (<1)	168
Rectal hemorrhage	0	-	0	-	1 (<1)	107
Fall	0	-	0	-	1 (<1)	389

Data Source: Table 1.42, Listing 1.4; NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.3 ISS, Table 2.28, Listing 2.4; NDA 022399, 01 May 2009, Sequence Number 0011, m5.3.5.3 120-Day SU, Table 4.30, Listing 4.4
Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

Seven patients reported new non-fatal, serious ADRs, after the 120-safety update. The final safety update contained a total of 20 non-fatal serious ADRs. This did not impact the original safety conclusion that GE is safe at a dose of 600 mg/day for the treatment of moderate to severe RLS. The non-fatal serious adverse drug reactions for patients participating in clinical trials of GE for the treatment of other indications were also included in Dr. Goldstein's review. There were no serious non-fatal ADRs that were suspicious for severe hypersensitivity reactions (SJS) or liver failure.

Adverse Reactions Leading to Withdrawal

The percentage of patients with RLS reported to have discontinued their respective clinical trials early because of an adverse drug reaction remain unchanged in the Final Safety Update compared to the percentage reported in the 120-day Safety Update. Somnolence and Dizziness were the two most common ADRs leading to withdrawal. The percentage of patients withdrawing early for RLS clinical trials remained stable at approximately 1% and 2% for somnolence and dizziness respectively.

Non-Serious Adverse Drug Reactions

Comparison of Common Adverse Drug Reactions (ADRs) By Safety Data Submission in The All RLS Dose Group (GSK Table)

Table 67 TEAEs Reported in at least 5% of Subjects in the GEn All Doses Group (Safety Population: All RLS Studies)

Preferred Term	Number (%) of Subjects		
	NDA Data Cut-off: 06 December 2007	120-Day SU Data Cut-off: 31 July 2008	FSU: 18 June 2010 Studies Complete
	GEn All Doses (N=1201)	GEn All Doses (N=1201)	GEn All Doses (N=1201)
Any event	**1009 (84)**	**1019 (85)**	**1024 (85)**
Somnolence	355 (30)	358 (30)	358 (30)
Dizziness	265 (22)	267 (22)	268 (22)
Headache	154 (13)	159 (13)	160 (13)
Nasopharyngitis	91 (8)	96 (8)	97 (8)
Nausea	87 (7)	92 (8)	90 (7)
Fatigue	79 (7)	83 (7)	83 (7)
Upper respiratory tract infection	47 (4)	56 (5)	58 (5)
Diarrhea	52 (4)	55 (5)	56 (5)

Data Source: Table 1.36; 1.32 NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.3 ISS, Table 2.8 and Table 2.12; NDA 022399, 01 May 2009, Sequence Number 0011, m5.3.5.3 120-Day SU, Table 4.25
Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

As noted by Dr. Goldstein, there were very few new ADRs reported in the Final Safety Update since the 120-day update. Overall, the updated information did not changes the safety profile of GE for treatment of patients with moderate to severe symptoms of RLS.

Non-Serious Adverse Drug Reactions Reported in Clinical Trials of GE for Other Indications

The incidence of non-serious ADRs were about the same or slightly less in the trials for patients in trials for the treatment of post-herpetic neuralgia, painful peripheral neuropathy and migraine prophylaxis. There was less somnolence reported by patients participating in non-RLS trials despite having received a higher dose of GE (1200 mg/day to 3600 mg/day) compared to patients in the RLS trials. Dizziness was reported with a similar frequency compared to patients treated with GE for RLS. Somnolence was reported at significantly lower rates in patients treated for migraine and post-herpetic neuralgia compared to patients treated for RLS, even those patients who received 1.5-6 times the dose. The increased reporting of somnolence in the patients treated

for RLS suggests that RLS patients may be more sensitive to the sedative effects of GE or it may be due to a difference in the trial designs.

PXN110748 Post-herpetic Neuralgia

Table 72 TEAEs Reported in at least 5% of Subjects (Safety Population: Study PXN110748)

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

Data Source: Table 5.9
All AEs occur more frequently than placebo in at least one active treatment arm.

MPX111381 Safety and Tolerability Study Migraine Headache Prophylaxis

Table 73 TEAEs Reported in at least 5% of Subjects (Safety Population: Study MPX111381)

Preferred Term	Number (%) of Subjects				
	PBO N=128	GEn 1200 mg N=66	GEn 1800 mg N=134	GEn 2400 mg N=133	GEn 3000 mg N=62
Any event	**87 (68)**	**44 (67)**	**99 (74)**	**101 (76)**	**49 (79)**
Dizziness	8 (6)	16 (24)	43 (32)	35 (26)	11 (18)
Fatigue	9 (7)	10 (15)	12 (9)	14 (11)	3 (5)
Nausea	12 (9)	3 (5)	15 (11)	12 (9)	6 (10)
Somnolence	6 (5)	6 (9)	7 (5)	14 (11)	9 (15)
Weight increased	7 (5)	4 (6)	8 (6)	9 (7)	4 (6)
Upper respiratory tract infection	9 (7)	4 (6)	4 (3)	9 (7)	5 (8)
Constipation	3 (2)	4 (6)	7 (5)	8 (6)	5 (8)
Dry Mouth	3 (2)	4 (6)	6 (4)	5 (4)	3 (5)
Nasopharyngitis	8 (6)	3 (5)	4 (3)	4 (3)	2 (3)
Diarrhea	8 (6)	1 (2)	1 (<1)	7 (5)	1 (2)
Vomiting	5 (4)	1 (2)	3 (2)	7 (5)	2 (3)
Influenza	4 (3)	1 (2)	3 (2)	4 (3)	3 (5)
Insomnia	1 (<1)	4 (6)	1 (<1)	6 (5)	2 (3)
Edema peripheral	4 (3)	4 (6)	1 (<1)	3 (2)	2 (3)
Sinusitis	3 (2)	4 (6)	3 (2)	3 (2)	1 (2)
Balance disorder	1 (<1)	2 (3)	2 (1)	6 (5)	1 (2)
Abdominal Pain	1 (<1)	2 (3)	2 (1)	3 (2)	3 (5)
Back pain	0	1 (2)	6 (4)	1 (<1)	3 (5)
Cough	0	3 (5)	1 (<1)	0	0

Source Data: Table 7.9
Note: TEAEs have been determined to be any AEs beginning during treatment (including up to 1 day after the last dose). AEs beginning prior to first dose of investigational product but worsening after first dose of investigational product are also considered to be TEAEs

Adverse Drug Reactions of Special Interest

Somnolence and Dizziness

The Change in The Percentage of Patients Reporting Somnolence from Week 1- Week 4 Long-term Trial XP-055 (GSK Table)

Table 31 Weekly Frequency of Somnolence and Dizziness TEAEs Based on Prior Exposure (Safety Population: Study XP055)

	Number (%) of Subjects		
Preferred Term	Naïve N=197	Non-naïve N=376	Total N=573
Week 1	n=197	n=376	n=573
Somnolence	44 (22.3)	28 (7.4)	72 (12.6)
Dizziness	32 (16.2)	7 (1.9)	39 (6.8)
Week 2	n=181	n=368	n=549
Somnolence	4 (2.2)	10 (2.7)	14 (2.6)
Dizziness	3 (1.7)	6 (1.6)	9 (1.6)
Week 3	n=172	n=364	n=536
Somnolence	4 (2.3)	4 (1.1)	8 (1.5)
Dizziness	2 (1.2)	1 (0.3)	3 (0.6)
Week 4	n=168	n=357	n=525
Somnolence	0	6 (1.7)	6 (1.1)
Dizziness	1 (0.6)	1 (0.3)	2 (0.4)

Data Source: DS Table 8.7

Note: Counts indicate the numbers of subjects reporting 1 or more events that map to the MedDRA system organ class or preferred term. At each level of summarization (system organ class or preferred term) subjects are only counted once. Events are treatment-emergent adverse events for XP055 only.

Among patients who remained in study XP-055 (open-label) by week 4, substantially fewer patients reported somnolence and dizziness at week 4 compared to week 1. Naïve patients reported both adverse reactions more frequently compared to non-naïve patients. The naïve patients also reported the greatest decline in somnolence and dizziness within the first 4 weeks after starting Horizant. The data reinforces the notion that the sedating effects of GE tend to resolve within the first few weeks of treatment in most patients who remain on treatment.

Effects of GE on Driving

There have been no additional studies performed to examine the potential effects of Horizant on driving. However, there is lingering concern that GE may impair the ability to drive safely for at least some time after starting the drug. The results of a simulated driving revealed that subjects who received 1200 mg/day of GE for 2 weeks had an increased lane position variability (LPV) and an increased number of simulated crashes. The increased (worse LPV) and increased number of simulated crashes reported in the 1200 mg/day GE group were similar to those reported in subjects given 50 mg diphenhydramine (active control) and tested at Tmax. Subjects tested after 2 weeks of treatment with 1800 mg/day performed similar to subjects who received placebo. The effect of 600 mg/day of GE on driving was not studied.

The concern is that 600 mg may effect on driving is similar to the effect associated with the 1200 mg/day dose of GE. Because of this concern, a postmarketing requirement was issued for the sponsor to study the effect of 600 mg/day of GE on driving. The study is a post-approval

requirement as opposed to a pre-approval study, because of the contradictory evidence indicating that the 1800 mg/day has essentially no adverse effect on driving.

Abuse Potential

The sponsor conducted a search of adverse reaction terms within its' clinical trails database seeking potential cases of abuse potential in association with GE. The search found a single case of a patient who reported experiencing withdrawal. The narrative for this patient noted he withdrew from chronically administered narcotic analgesics administered for back pain. The patients suddenly stopped taking all of his prescribed pain medications that included regular dose of narcotics and GE without informing his physician. He was subsequently treated in a local emergency room for symptoms of narcotic withdrawal.

Clinical Trials Database Search for Adverse Event Terms Suggestive of Abuse (GSK Table)

Table 132 Abuse Potential TEAE Search Results (Safety Population: All RLS)

	Number (%) of Subjects	
	NDA Data Cut-off: 06 December 2007	FSU: 18 June 2010
	GEn All Doses (N=1201)	GEn All Doses (N=1201)
Any Event	47 (4)	51 (4)
Feeling Drunk	25 (2)	25 (2)
Euphoria	8 (<1)	8(<1)
Feeling Drugged	8 (<1)	8(<1)
Mood Swings	5 (<1)	9 (<1)
Feeling Abnormal	1 (<1)	1 (<1)
Accidental Overdose	1 (<1)	0[1]
Withdrawal Syndrome	0	1 (<1)

Data Source: Table 1.68; NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.3 ISS, Table 5.61

1. The overdose event 'accidental overdose or over medicated' for Subject 128 5010 which was present in the ISS database is no longer present in the FSU database.

8. Advisory Committee Meeting

The decision was made not to present this application to an advisory committee based on several reasons:

- GE is rapidly converted to gabapentin in enterocytes and almost all of the drug entering the circulation is gabapentin derived from GE.
- The safety of approved gabapentin is established at doses resulting in exposures above those associated with the recommended dose for GE.
- The sponsor of GE has established the product is effective at a dose of 600 mg/day for moderate to severe symptoms of RLS in adults.

9. Pediatrics

Waiver to study GE in children with primary RLS below the age of 13 years.

The sponsor requested and was granted a waiver under PREA by PeRC from a requirement to study GE in children below the age of 13 years. The waiver was granted because it is not feasible to complete studies in this age group for the following reasons.

- Children in this age group have a low prevalence of clinically significant RLS symptoms in this population.
- There is a lack of information about the clinical course of RLS and the belief that RLS is intermittent with asymptomatic periods.
- Published literature indicating that non-pharmacological treatments are recommended for treatment of RLS in this population in most cases.
- There is a lack of extensive validation of the consensus diagnostic criteria for RLS in this population in the clinical setting.
- There is a lack of a validated diagnostic instrument for RLS in this population.
- There is a lack of a validated disease-specific symptom severity rating scale in this population.

Pediatric Deferral

- The sponsor was granted a deferral to study adolescents from ages 13 to 61years 11 months (age 17) until it can be determined if lower dosages are effective in treating adults with RLS.
- The Pediatric Postmarketing Requirements are listed in Section 12 of this review.

10. Other Relevant Regulatory Issues

- 505(b)(2) Assessment entered in DARRTS 3/30/11 with no outstanding issues

11. Labeling

- Proprietary name- final DMEPA review in DARRTS on 3/28/11 the name is acceptable.

- Label and Medication Guide revised during at a face to face meeting with the reviewers from DDMAC and DRISK.
- Prescriber labeling reviews from DDMAC and DRISK are complete and in DARRTS. A review by SEALD not required for this application.
- Carton and immediate container labels final review of the 3/15/11 complete and accepted by sponsor and OSE (confirmed 4/4/11).

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

<u>Approval</u> for the 600 mg/day tablet taken once a day at 5 PM for the treatment of the symptoms of primary, moderate to severe RLS in adults.

Risk Benefit Assessment

Overall, the 600 mg dose of GE is effective and safe for the targeted population. However, the effects of the 600 mg dose of GE on driving are unknown. The results of study XP083 indicate the 1200 mg/day dose causes an increase in lane position variability (poor performance) and an increased number of simulated crashes compared to subjects who received placebo or diphenhydramine (positive control). Subjects given Horizant 1800 mg/day did not perform differently on simulated driving tasks compared with subjects in the placebo group. The effect of 600 mg of Horizant has on driving performance will be studied as a postmarketing requirement.

Pediatric studies were deferred until lower tablet strengths of Horizant are developed. Although, the 600 mg/day dose is effective for reducing the symptoms of primary RLS, the effect reached a plateau at or below 600 mg/day. The sponsor has agreed to study the efficacy of lower doses of Horizant, 300 mg/day and 450 mg/day in comparison to the 600 mg/day dose in adults as a postmarketing commitment. Once the maximally effective lowest dose of Horizant is identified in adults, it can be used to select an appropriate dose(s) to study the treatment of RLS in adolescents. Because children in their mid to late teen years are learning to drive, a postmarketing requirement to study the effects of Horizant on driving in children ages 15-17 was included in the approval.

The agency's interpretation of the carcinogenicity data in animals was integral to the approval. The sponsor was unable to demonstrate that a mechanism unique to rats or a specific strain of rats was responsible for development of pancreatic acinar tumors in animals that are not a concern for humans taking gabapentin. The margin between the no tumor effect level in animals and the exposure associated with the recommended human dose (600 mg/day) can be interpreted as being as small as 8 fold (at an animal dose of 500 mg/kg/day) versus as large as 25 fold (at an animal dose of 1000 mg/kg/day). The sponsor's reanalysis of the gabapentin and Horizant carcinogenicity study produced a reasonable argument for considering the 1000 mg/kg/day dose as the no effect dose for pancreatic acinar carcinoma.

The epidemiological studies were designed and analyzed adequately but the studies were limited by too few patients within the GPRD database with long-term use of gabapentin. If the epidemiological data offers any reassurance, it is that relatively few patients remain on gabapentin for years.

Postmarketing Risk Evaluation and Management Strategies

OSE and DNP agree that a Medication Guide for Horizant will required but it will not be required under a REMS.

Postmarketing Requirements and Commitments

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

Final Protocol Submission: 01/2015
Study/Trial Completion: 06/2016
Final Report Submission: 06/2017

2 Conduct a double-blind, randomized, placebo-controlled, parallel group efficacy and safety evaluation trial in adolescents =13 years to17 years with moderate to severe symptoms of Primary Restless Legs Syndrome.

Final Protocol Submission: 06/2105
Study Completion: 10/2023
Final Report Submission: 10/2024

3 Conduct a long-term safety trial 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 #2.

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

4 Conduct a driving trial in adolescent patients of legal driving age who have Restless Legs Syndrome, using diphenydramine as active control.

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

5. 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 study according to the following schedule:

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

6 A simulated driving trial in healthy adult subjects treated with an appropriate dose of gabapentin enacarbil determined in PMR #8 that includes active comparator and placebo arms.

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

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

7 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

8 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
Study Completion:	07/2014
Final Report Submission:	02/2015

9 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 Report Submission: 06/2011

10 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

11 A clinical drug-drug interaction trial to evaluate the pharmacokinetic 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

PMC

12 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:

(b) (4)

REFERENCES

1. Friedman GD, Udaltsova N, Chan J, Quesenberry CP, Habel LA. Screeningpharmaceuticals for possible carcinogenic effects: initial positive results for drugs notpreviously screened. *Cancer Causes Control.* 2009;20:1821–1835.

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/s/

GERALD D PODSKALNY
04/05/2011