# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022399Orig1s000

# SUMMARY REVIEW

# Deputy Office Director Decisional/Approval Memo

| | |
|---|---|
| **Date** | 4/6/11 |
| **From** | Ellis F. Unger, M.D.<br>Deputy Director, Office of Drug Evaluation-I |
| **Subject** | Office Director Decisional Memo |
| **NDA/BLA #**<br>**Supplement #** | 22-399<br>0000/0045 |
| **Applicant Name** | GlaxoSmithKline |
| **Date of Submission** | 9/16/08; resubmission 1/9/09; response to CR 10/6/11 |
| **PDUFA Goal Date** | 4/6/11 |
| **Proprietary Name /**<br>**Established (USAN) Name** | Horizant<br>gabapentin enacarbil |
| **Dosage Forms / Strength** | 600-mg extended-release tablets |
| **Proposed Indication(s)** | Restless Legs Syndrome |
| **Action:** | Approval |

| **Material Reviewed/Consulted**<br>Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Project Manager | Beverly A. Conner |
| Cross-Discipline Team Leader | Gerald D. Podskalny |
| Medical Officer | Susanne R. Goldstein |
| Biostatistical Review | Sharon Yan, Kun Jin, James Hung |
| Pharmacology Toxicology Review | Terry S. Peters, LuAnn McKinney, Lois M. Freed, Paul C. Brown |
| Chemistry Manufacturing Controls | Chhagan G. Tele, Martha Heimann, Christine M. V. Moore |
| Clinical Pharmacology Review | Ju Ping Lai, Seongeun (Julia) Cho, Atul Bhattaram, Angela Men, Yaning Wang |
| Carcinogenicity/Statistical | Karl K. Lin, Steven Thomson |
| Division of Scientific Investigations | Antoine N. El Hage |
| Office of Surveillance and Epidemiology (OSE): Division of Medication Error Prevention and Analysis | Zachary Oleszczuk, Anne Crandall, Melina Griffis |
| OSE, Division of Epidemiology | James R. Williams, Simone Pinheiro |
| Office of Pharmaceutical Science | Raanan Bloom |

I concur with the recommendation of Dr. Russell Katz, Director, Division of Neurology Products, on the approval of Horizant (gabapentin enacarbil) for the treatment of moderate to severe Restless Legs Syndrome (RLS). The review team is in agreement with the planned action.

Background: The Office of Drug Evaluation-I took a Complete Response action to the original New Drug Application (NDA) submission on 2/17/10, based on findings of pancreatic acinar cell tumors in a 2-year carcinogenicity study in rats. The no-effect dose of 500 mg/kg/day in male rats was associated with a plasma AUC only ~ 8-fold the human AUC at the to-be-marketed dose of 600 mg/day. Other aspects of the application, in particular, Chemistry Manufacturing Controls (CMC), clinical pharmacology, clinical efficacy, clinical safety, and inspections, were found to be acceptable.

We provided the applicant with several suggested pathways to address the carcinogenicity findings, and met face-to-face for discussion. These lines of reasoning included:

1. showing that the rat data are not relevant to humans;
2. demonstrating efficacy with lower doses of gabapentin enacarbil, which would increase the safety margin between human and rat exposure;
3. providing strong reassurance regarding the risk of cancer, based on gabapentin's post-marketing data; and
4. showing that gabapentin enacarbil imparts some advantage over existing therapies for RLS, presumably by studying patients who are non-responders or poor responders to the approved drug(s). (Such studies could lead to a claim for second-line use.)

The applicant's Complete Response is focused on options 1 and 3, above. Importantly, however, the applicant reclassified the NDA as a 505(b)(2), with Neurontin as the reference listed drug [the original NDA was filed under 505(b)(1)]. Use of data from the Neurontin label, along with generation of new bridging toxicokinetic data, enabled the applicant to develop a new safety margin – higher than the margin in the original NDA.

Thus, the focus of review activities on the Complete Response is principally limited to consideration of these new arguments.

Restless Legs Syndrome (RLS) is a relatively common and frequently underdiagnosed sensorimotor disorder with an estimated prevalence between 5 and 10%. Its prevalence increases with age and is higher among women than men. A family history of RLS is particularly common, especially in patients whose symptoms appear before age 40. The cardinal feature of RLS is a distressing, overwhelming urge to move the legs (akathisia), which often coexists with a deep discomfort within the legs. Symptoms typically begin or worsen during periods of rest or inactivity, e.g., lying or sitting, and worsen in the evening or night. Symptoms are partially or completely relieved by movement, such as walking or stretching.

There are two approved drugs for the treatment of moderate to severe RLS – ropinirole (Requip®) and pramipexole (Mirapex®); both are dopaminergic agents. Gabapentin, an antiepileptic agent approved for the treatment of seizures and post-herpetic neuralgia, is used off-label for RLS, and its use is included in current RLS treatment guidelines (at doses of 300 to 2700 mg per day). Generic versions of gabapentin are available in the U.S. Benzodiazepines and opiates are used off-label for RLS as well.

Chemistry Manufacturing Controls: Gabapentin enacarbil is a pro-drug of the marketed drug gabapentin. The Chemistry Manufacturing Controls (CMC) data were reviewed in the original submission. We did not request additional data in our Complete Response, and none were submitted. In the original submission, the applicant provided adequate information regarding structure elucidation and confirmation, method of manufacture, in-process controls, test methods, container closure system, and stability testing of the drug substance. The drug product was deemed satisfactory, and the Chemistry review team opined that Horizant (extended-release) ER Tablets could be approved from their point of view.

Pharmacology/Toxicology: The pharmacology/toxicology findings in the original NDA submission provided the basis for the review team's recommendation to take a Complete Response action. The key findings were extensively discussed by members of the review team at the time, and are summarized below.

Gabapentin enacarbil is a pro-drug of gabapentin, and virtually all of the pro-drug is converted to gabapentin by first-pass hydrolysis. Gabapentin's carcinogenicity data are, therefore, germane to this NDA. At the time gabapentin was approved as an anti-epileptic drug (AED), it was known to cause a statistically significant increase in the incidence of pancreatic acinar cell carcinoma in male rats. The no-effect dose was 1000 mg/kg, a dose that would produce a peak plasma concentration 6.5 times higher than would be produced in humans receiving a daily gabapentin dose of 3600 mg. Gabapentin was approved despite this relatively low margin, in part because of the serious nature of the disease to be treated (epilepsy). Moreover, particular factors provided reassurance regarding the non-clinical findings: carcinoma were observed in only one sex, they were not locally invasive, and they neither metastasized nor shortened survival. The drug was approved with a warning regarding "tumorigenic potential," citing "…an unexpectedly high incidence of pancreatic acinar adenocarcinomas…in male, but not female, rats," followed by a statement that the clinical significance of the finding is unknown.

With respect to the data included in the original gabapentin enacarbil NDA, the drug was not genotoxic in a standard battery of genetic toxicology assays, and the mouse carcinogenicity study was negative. The 2-year carcinogenicity study in rats, however, demonstrated dose-related pancreatic acinar cell carcinoma, as well as dose-related adenomas and hyperplasia, as summarized below:

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg/d) | 0 | 500 | 2000 | 5000 | 0 | 500 | 2000 | 5000 |
| Hyperplasia | 14/60 | 10/60 | 14/60 | 20/60 | 1/60 | 1/60 | 4/60 | 14/60 |
| 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 |

The increases were statistically significant in males and females at 5000 mg/kg/day, with a suggestive trend in males at 2000 mg/kg/day. The no-effect dose of 500 mg/kg/day was associated with a plasma AUC in males that was only ~ 8-fold the human AUC at the clinical dose of 600 mg/day.

The review team had additional concerns. The carcinoma observed in both sexes were locally invasive (in contrast, the tumors in the gabapentin NDA were observed exclusively in

males and were not locally invasive). Also of concern, male rats in the 2000 and 5000 mg/kg/d groups were killed 7 and 14 weeks prior to the planned conclusion of the 104-week study, and the review team pointed out that additional tumors might have been detected had the rats been maintained for the planned duration of the study. (In males, the 2000 and 5000 mg/kg/d groups were terminated early because of increased mortality caused primarily by chronic progressive nephropathy.)

The no-effect doses for carcinoma were 500 and 2000 mg/kg/d in male and female rats, respectively, corresponding to AUCs approximately 8- and 28-times the exposure in humans at a dose of 600 mg qd.

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. Although the difference in tumor type was appreciated by the review team, there was inadequate information to establish that these tumors were not clinically relevant.

*Applicant's Response:*

The applicant provided a number of arguments to address the carcinogenicity concern regarding the pancreatic acinar cell tumors in rat, and these arguments were carefully considered by Drs. McKinney, Freed, and Brown.

1. Relevance of Pancreatic Acinar Cell Tumors to Humans

The applicant argued that the pancreatic tumors observed in rats are not relevant to humans. They noted that the rat tumors were of pancreatic acinar cells and that such tumors occur spontaneously in the rat, whereas the majority of human of pancreatic tumors are ductal in origin. They also opined that the rat is uniquely sensitive to gabapentin-induced pancreatic acinar cell tumors, possibly because of greater uptake of gabapentin into the pancreas, as evidenced by an unusually high spontaneous rate of these tumors in rats. They also posited that male rats are particularly sensitive to gabapentin-induced pancreatic acinar cell tumors because of differential effects of male and female sex hormones.

The pharmacology/toxicology review team did not find these arguments to be compelling. They noted that the relevance of the difference in pancreatic cell types is speculative: the processes involved in pancreatic regeneration and cellular proliferation are not well-understood, and the cellular origins of pancreatic tumors in animals and humans remain uncertain. The review team cited published studies suggesting that all pancreatic cell types have the potential to undergo phenotypic change, giving rise to different cells within the pancreas (e.g., acinar to ductal; islet to ductal). Moreover, the sponsor's *in vitro* data demonstrate a greater presence of a high-affinity gabapentin transporter (LAT1) in human pancreatic islet cells, suggesting that gabapentin may preferentially concentrate in human islet cells. This transport mechanism, coupled with gabapentin's mitogenic effect, could lead to a variety of pancreatic tumors in humans. With respect to the applicant's argument that the rat (particularly the male) is more sensitive to drug-induced pancreatic tumors than human, based on interspecies differences in the spontaneous rates of pancreatic acinar cell tumors and demonstrated responsiveness of rat pancreas to various agents, the review team noted that gabapentin enacarbil was clearly tumorigenic in female rats, and that the spontaneous incidence of pancreatic acinar cell tumors in female rats is very low.

2. Exposure Margin

Based on the data in the original submission, the applicant did not disagree with the safety margin of 8 calculated by CDER. In their Complete Response, however, they provided new data and advanced a number of arguments, based on disparate lines of reasoning, to support an exposure margin greater than 8.

First, they argued that the historical control information should be based, not on Wistar and Wistar:Han rats, but on the Wistar rat alone. Using only the Wistar rat as the historical control, the margin of safety would be 38. For a variety of reasons outlined in her review, however, Dr. McKinney rejected this argument.

Second, the applicant argued that the ratio of pancreatic/plasma drug levels is higher in rats than in humans, such that for any given safety margin calculated on the basis of plasma concentrations, the safety margin in pancreas would be greater. The applicant conducted an *in vitro* study to assess accumulation of $^{3}$H-gabapentin in rat and human pancreatic slices, as well as an *in vitro* study to assess the expression and localization of gabapentin transporter proteins in mouse, rat, and human pancreas. Considering the new data on relative pancreatic accumulation of gabapentin in human and rat pancreas, the applicant concluded that the margin of safety was >50-fold. For a number of reasons, however, the review team did not find the *in vitro* data to be compelling, and rejected this line of reasoning.

One line of reasoning was deemed to be convincing by the pharmacology/toxicology review staff:

As noted above, the applicant now refers to the Agency's finding for gabapentin (Neurontin), the reference listed drug. The 2-year lifetime carcinogenicity study of gabapentin in rat showed the same tumor finding, and 1000 mg/kg/day was determined to be a “no-effect” dose for carcinoma. The sponsor provided toxicokinetic bridging data obtained under conditions similar to those used in the original gabapentin rat carcinogenicity study, at doses of 1000 and 2000 mg/kg/day. The gabapentin exposure (AUC) in the rat at the NOAEL (1000 mg/kg) was approximately 25-times higher than the human exposure from gabapentin enacarbil at the to-be-labeled maximum recommended daily dose of 600 mg.

This safety margin of ~25 is considerably higher than the previous margin of 8, which was based on a NOAEL of 500 mg/kg/day for gabapentin enacarbil in the rat study. Although there is no clear guidance on an acceptable safety margin for carcinogenicity, the pharmacology/toxicology review team opined that a 25-fold margin between plasma exposure at the high dose used in a lifetime rat carcinogenicity study and that in humans at the maximum recommended daily dose suggests lesser concern for humans.

3. Epidemiological data do not support a carcinogenic effect of gabapentin in humans

Because gabapentin has been marketed since 1993, there is the opportunity to assess the numbers of spontaneous reports of pancreatic cancer during the post-marketing period. The Sponsor conducted two parallel nested-case control studies in the United Kingdom General Practice Research Database (GPRD) to examine associations between gabapentin exposure and a number of cancer outcomes. These studies were carefully reviewed by Dr. James Williams, Division of Epidemiology, OSE. He opined that neither a previously submitted study from Kaiser Permanente Northern California nor the GPRD studies provide evidence of a causal association between gabapentin use and cancer, in particular pancreatic and renal

cancers. Although the studies were well-conceived and well-conducted, the strength of their findings was limited by the small number of patients with chronic gabapentin exposure.

The first study examined associations between gabapentin exposure and the incidence of pancreatic and renal cancers in all patients exposed to gabapentin between 1/1/93 and 12/31/08 (16 years). Using the same design as the first, a second study also examined associations between gabapentin exposure and the incidence of pancreatic and renal cancers, but also assessed malignancies at a number of other body sites. (The latter study excluded patients with previous cancer diagnoses.) In both studies, cases were risk set-matched with up to 10 controls for sex, age, year of cohort entry, and general practice site.

There were statistically significant associations between gabapentin exposure and pancreatic and renal cancer 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. Although these studies provided some evidence of an association between gabapentin exposure and incident cancer, the findings were weakened by a number of considerations.

First, the association between gabapentin exposure and cancer was not dose-related. There was a statistically significant association for only the lowest tertile of exposure. A positive correlation between increasing exposure and risk would have made the finding more compelling. Second, exposures to gabapentin were brief: the duration of use of the first tertile spanned from 0 to 1.6 months and the number of prescriptions of the first tertile from 1 to 2 prescriptions. Moreover, the median latency between first gabapentin exposure and incidence was 416 days for renal cancer and 573 days for pancreatic cancer, but the latency period was 100 days in 25% of pancreatic cancer cases and in 31% of renal cancer cases. The detection of a macroscopic cancer in response to 1 to 2 doses of a small molecule after a duration of 100 days defies the known principles of tumor biology! Third, the statistically significant associations observed were thought likely to be an artifact of a protopathic bias, or potentially a surveillance bias. Post-hoc review of gabapentin use in pancreatic and renal cancer cases in the first GPRD study revealed that 14% of pancreatic and 31% of renal cancer cases had had gabapentin prescribed for the treatment of paraneoplastic syndromes, or had a clinical suspicion of cancer prior to initial gabapentin exposure – presumably confirmed after subsequent diagnostic testing. It is also possible that patients who receive gabapentin prescriptions more frequently report symptoms that trigger diagnostic tests that would identify pancreatic cancer more often than patients who do not receive gabapentin.

Overall, Dr. Williams opined that the two GPRD studies suggest that any association between limited gabapentin exposure and cancer is most likely explained by protopathic bias or potentially a surveillance bias. Importantly, given the brief duration of gabapentin use characteristic of typical current clinical practice, these studies cannot address the potential carcinogenicity associated with chronic gabapentin enacarbil use.

If gabapentin enacarbil is approved, The Division of Epidemiology, OSE does not recommend further evaluation of gabapentin enarcarbil's carcinogenicity by means of an observational post-marketing requirement. They noted: "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."

Clinical Pharmacology: Unlike gabapentin, which is absorbed exclusively in the small intestine via a saturable amino acid transporter, gabapentin enacarbil is efficiently absorbed by high capacity transport mechanisms found throughout the intestinal tract. The pro-drug is rapidly and virtually entirely converted to gabapentin, leaving only negligible amounts (<2%) of circulating parent drug. The pharmacokinetics of gabapentin are linear when the pro-drug (gabapentin enacarbil) is given over a range of doses up to 6 g.

Gabapentin is not appreciably metabolized. Neither gabapentin enacarbil nor gabapentin is a substrate, inhibitor, or inducer of the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). It is not known if gabapentin enacarbil is a substrate, inhibitor, or inducer of CYP2B6 or CYP2C8, but this will be studied as a post-marketing requirement.

Evidence of Effectiveness: The evidence of effectiveness was addressed by Drs. Goldstein, Yan, Podskalny, and Katz in their review of the original submission. No new efficacy data were included in the applicant's Complete Response.

The applicant submitted data from three randomized controlled trials to establish gabapentin enacarbil's evidence of effectiveness for the treatment of moderate to severe RLS. The key trials included two standard, parallel-group randomized, controlled trials: one (Trial 52) compared gabapentin enacarbil 1200 mg daily to placebo, and the other (Trial 53), a 3-armed study, compared two doses of gabapentin enacarbil (600 and 1200 mg daily) to placebo. There was also a randomized withdrawal trial (Trial 60) to assess gabapentin enacarbil's long-term effectiveness in responders, and an exploratory 5-armed trial (Trial 81) comparing 4 doses of gabapentin enacarbil (600 to 2400 mg/day) to placebo.

Trials 52 (n=222) and 53 (n=325) were multicenter, randomized, double blind, placebo-controlled, 12-week trials in subjects with moderate to severe RLS. In Trial 52, subjects were randomized to receive daily doses of gabapentin enacarbil 1200 mg or placebo. Trial 53 was an identically-designed study comparing gabapentin enacarbil 1200 mg/day to placebo, except that a lower-dose arm (600 mg) was added in an early protocol amendment in response to the Division's recommendations. Each arm was to enroll 105 subjects. The study drug was to be taken daily at 5 PM in both studies.

The trials had identical co-primary endpoints of: 1) International Restless Legs Scale (IRLS) score, a patient-rated 10-item score (summed score 0 [asymptomatic] to 40 [worst]) - change from baseline to end-of-treatment; and 2) proportion of responders based on the Clinical Global Impression of Improvement (CGI-I) scale, a 7-category scale that requires the investigator to assess how much the patient's illness has improved or worsened relative to baseline. Categories include: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. Subject who were rated as "very much improved" or "much improved" were categorized as "responders." The change from baseline in IRLS total score was analyzed by analysis of covariance (ANCOVA) including effects for pooled site, treatment, and the baseline value as covariates. The response to treatment from the Investigator-rated CGI of Improvement at the end of treatment was analyzed using a logistic regression model that included treatment and pooled site as explanatory factors.

The 1° efficacy analysis was conducted on a modified ITT (MITT) population, defined as all patients in the Safety Population who completed the IRLS rating scale at baseline and had at least one on-treatment IRLS rating scale score. The population was analyzed as randomized. The coprimary endpoints were each tested at the 0.05 significance level. Only if *both* tests were statistically significant was the study to be considered to have provided evidence of efficacy.

Of note, these metrics were also used in the registrational trials for ropinirole and pramipexole.

Trial 52 Results: A total of 222 subjects were randomized (114 gabapentin enacarbil; 108 placebo). Approximately 86% of subjects completed the trial in both groups, and essentially all were included in the modified ITT analysis. The mean change in the IRLS score from baseline to Week 12 was -13.2 in the gabapentin enacarbil group and -8.8 in the placebo group ($p=0.0003$). The proportions of responders on the investigator-rated CGI-I Scale at Week 12 were 76.1% in the gabapentin enacarbil group compared with 38.9% in the placebo group ($p<0.0001$).

Trial 53 Results: A total of 325 subjects were randomized (113 gabapentin enacarbil 1200 mg, 115 gabapentin enacarbil 600 mg, 97 placebo). Completion rates for the gabapentin enacarbil 1200 mg, 600 mg, and placebo groups were 87%, 90%, and 79%, respectively. A total of 111 subjects in the 1200 mg group, 114 in the 600 mg group, and 96 in the placebo group were included in the primary analysis.

The mean change from baseline to Week 12 for the IRLS score was -13.0 in the gabapentin enacarbil 1200 mg group, -13.8 in the gabapentin enacarbil 600 mg group, and -9.8 in the placebo group (1200 mg vs. placebo: $p<0.002$; 600 mg vs. placebo: $p<0.0001$). The proportions of responders on the CGI-I Scale at Week 12 were 77.5% for the gabapentin enacarbil 1200 mg group, 72.8% for the gabapentin enacarbil 600 mg group, and 44.8% in the placebo group (1200 mg vs. placebo: $p<0.0001$; 600 mg vs. placebo: $p<0.0001$). Of note, 41% of subjects were male, and no treatment effect was evident in males on the IRLS rating scale endpoint: IRLS change from baseline to Week 12 was -10.4, -11.9, and -10.4 for placebo, gabapentin enacarbil 600 mg, and gabapentin enacarbil 1200 mg, respectively. Conversely, results on the CGI-I responders analysis were robust in both sexes.

Trial 60 was a randomized withdrawal trial, designed to demonstrate long-term effectiveness of gabapentin enacarbil. All subjects were to receive gabapentin enacarbil 1200 mg daily for 24 weeks (single-blind). After completion of the single-blind treatment, “responders” were randomized to receive either gabapentin enacarbil 1200 mg/d or placebo for 12 weeks in double-blind fashion.

The definition of a “responder” included the following:

- completed the entire 24-week single-blind treatment period
- total IRLS score decreased by $\geq 6$ points relative to baseline, and $\leq 15$
- categorized as “much improved” or “very much improved” on the CGI-I
- stable on 1200 mg gabapentin enacarbil for $\geq 1$ month

The 1° outcome was the proportion of patients who met criteria for a relapse during the 12-week double-blind phase. Relapse criteria were defined as: 1) an increase in IRLS score of ≥ 6 points compared to Week 24, resulting in an IRLS score of ≥ 15, and a rating of "very much worse" or "much worse" on the CGI-I. These criteria had to have been met on ≥ 2 consecutive visits ≥ 1 week apart, or 2) withdrawal due to lack of efficacy.

Of 327 subjects originally enrolled in the trial, 194 (59%) met responder criteria during the 24-week single-blind phase and were randomized to continue gabapentin enacarbil (n=96) or switch to placebo (n=98). The proportions of subjects who met criteria for relapse were 9.4% in the gabapentin enacarbil group and 22.7% in the placebo group ($p<0.02$), providing support for the long-term effectiveness for the 1200 mg daily dose.

Trial 81 was an exploratory, multicenter, randomized, double-blind, multiple fixed-dose study wherein patients with RLS were randomized to receive placebo, or gabapentin enacarbil 600, 1200, 1800, or 2400 mg daily for 12 weeks. The protocol did not specify 1° or 2° outcomes, but the review team analyzed the endpoints designated as 1° in trials 52 and 53.

A total of 217 patients were randomized; results are shown below:

Change from Baseline in mean IRLS Score:

| | n | Baseline | End of Study | P-value |
|---|---|---|---|---|
| Placebo | (n=40) | 22.45 | -9.28 | |
| Gabapentin enacarbil 600 | (n=47) | 23.87 | -13.81 | 0.04 |
| Gabapentin enacarbil 1200 | (n=43) | 23.91 | -13.81 | 0.04 |
| Gabapentin enacarbil 1800 | (n=37) | 23.62 | -13.95 | 0.026 |
| Gabapentin enacarbil 2400 | (n=44) | 23.34 | -12.86 | 0.09 |

Proportion of Responders:

| | Proportion of Responders | P-value |
|---|---|---|
| Placebo | 45% | |
| Gabapentin enacarbil 600 | 64% | 0.08 |
| Gabapentin enacarbil 1200 | 65% | 0.07 |
| Gabapentin enacarbil 1800 | 73% | 0.01 |
| Gabapentin enacarbil 2400 | 82% | 0.0005 |

The study was neither designed nor powered to show differences in treatment effects between doses, but the results do provide some support of efficacy. Interestingly, there is no apparent trend to support the concept that doses higher than 600 mg/d lead to greater efficacy.

Efficacy Summary

As it was after review of the original NDA data, all on the review team agree that the trials demonstrate satisfactory evidence of efficacy for the 1200 mg/day and 600 mg/day doses of gabapentin enacarbil. The trials were appropriate in design, reasonable in duration, utilized standard endpoint measures (measures that were used to establish efficacy for the two drugs currently approved for RLS), and enrolled subjects that seem relevant to the "real world." The statistical analyses were performed as prospectively planned, and the results were reasonably persuasive. The results of both of the randomized, double-blind, placebo-controlled trials (52 and 53) were similar: in the gabapentin enacarbil groups, mean improvement on the IRLS score was approximately 4 points greater (absolute) than placebo. In both studies, there was a striking treatment effect in the responder analysis: approximately 40% of subjects in the placebo group were categorized as responders, compared to 75% in the gabapentin enacarbil groups. There were no apparent irregularities in trial conduct that would call the study results into question.

There was no evidence that the 1200 mg/day dose conferred any advantage over the 600 mg/day dose. The review team opined that only the lower dose should be considered for approval. I agree with this recommendation.

Clinical Safety:

The applicant's Complete Response included additional safety data on completed subjects in an open-label extension study, as well as summary data on clinical safety from studies of gabapentin enacarbil used in RLS-associated sleep disturbances, pain in diabetic peripheral neuropathy, post-herpetic neuralgia, migraine prophylaxis.

There were 3 deaths in the development program: a completed suicide in a 51 year-old male 36 hours after receiving a single 1200 mg dose of gabapentin enacarbil in a clinical pharmacology study; a 48 year-old male whose body was found at the bottom of an overpass (a possible suicide) 26 days after completing a course of gabapentin enacarbil; and a 63 year-old female who died after aspirating a piece of meat. Given that suicide is a known concern with AEDs, and that gabapentin enacarbil is a prodrug of gabapentin, an AED, the deaths in the two male subjects are concerning; however, causality is unlikely in both cases: the 51 year-old male received only 1 dose of gabapentin enacarbil, and the 48 year-old male had been off of the drug for 26 days at the time of the event.

Sedation (and somnolence) is a major untoward effect of gabapentin enacarbil. Gabapentin is known to cause somnolence, and somnolence was clearly detected in the development program at a frequency of approximately 20% on drug and 5% on placebo. It accounted for half of the subjects who withdrew from clinical trials because of an adverse event.

Driving ability was assessed in Trial 83 using a computer-based driving simulation system. Healthy volunteers were randomized 1:1:1:1 to receive, at 5 PM, placebo, gabapentin enacarbil 1200 mg, gabapentin enacarbil 1800 mg, or diphenhydramine 50 mg (an active control used to gauge assay sensitivity). Participants randomized to diphenhydramine were tested near its $T_{max}$. Of note, the 600 mg dose was not assessed in the trial. The assessed endpoints were variation in lane position and virtual "crashes."

After a 5 PM dose, 1200 mg gabapentin enacarbil impaired driving ability, during both the following morning and evening (when patients may be driving to and from work, respectively). The impairment tended to be worse than that caused by diphenhydramine, the positive control.

Three critical issues were not addressed by the trial: 1) The 600 mg dose was not tested; therefore, it is not known to what extent, if any, the "approvable" dose would impair driving. 2) The time course of somnolence was not characterized with respect to time of gabapentin enacarbil administration. Specifically, no assessment was made until more than 12 hours post-dose. The extent to which gabapentin enacarbil affects cognitive performance at times closer to its $T_{max}$ of 5-7 hours, from 5 PM to bedtime, is unknown. Third, driving impairment was tested only after 2 weeks of treatment. The effects more proximal to initiation of therapy, and effects after longer periods, are unknown. These issues are to be addressed as post-marketing requirements.

**Post-marketing Requirements and Commitments**

Additional safety issues identified by the review team will be address through post-marketing requirements under Section 505(o)(3) of the FDCA. These include:

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

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

3. An adequate, randomized, double-blind, placebo- and moxifloxacin-controlled trial to evaluate the effect of gabapentin enacarbil on cardiac repolarization in healthy adult subjects (a thorough QT study).

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

There will also be post-marketing commitments:

1. 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.

2. 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.

**Summary and Conclusions**

The applicant has established efficacy using standard clinical trial methodology, and the results seem to be solid. The individual efficacy trials (52 and 53) demonstrated statistically significant treatment effects on both of their co-primary endpoints – a fairly conservative criterion for success. Considering efficacy in its most positive light, Trials 52 and 53 showed that the percentages of subjects judged as “very much improved” or “much improved” by their investigators were approximately 40% in the placebo group, versus approximately 75% in the gabapentin enacarbil groups. As noted above, differences in changes in IRLS scores were also statistically significant in both trials.

The clinical safety profile is reasonably well-characterized, although there are important gaps in knowledge regarding somnolence and driving ability, the latter to be assessed through post-marketing requirements. Based on data-in-hand, driving ability is a major safety concern, and it is emphasized in labeling. The other principal risks are suicidality – associated with taking anti-epileptic drugs – and dizziness. (Gabapentin enacarbil is a prodrug for gabapentin, an anti-epileptic drug.) These important risks will be mitigated through labeling and mandatory distribution of a Medication Guide. The review team opined that a communication plan was not warranted; therefore, a REMS is no longer a requirement. The original requirement for a REMS will be retracted through a separate memorandum.

As described above, the risk of cancer has been adequately addressed through referral to the gabapentin NDA, the reference listed drug, and newly-developed toxicokinetic bridging data.

Based on all of the above, I concur with the planned approval action of the Division of Neurology Products (DNP), and hereby approve gabapentin enacarbil extended-release tablets for the treatment of moderate to severe primary RLS in adults.

---

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

---

/s/

---

ELLIS F UNGER
04/06/2011