CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022399Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

COMPLETE RESPONSE

NDA 022399

Glaxo Group Limited
d/b/a GlaxoSmithKline
Attention: Debra Lake, M.S.
Manager, U.S. Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your new drug application (NDA) dated January 8, 2009, received January 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Horizant (gabapentin enacarbil) Extended-Release Tablets 600 mg.

We also acknowledge receipt of your amendments and correspondence dated:

January 14, 2009
February 20, 2009
February 25, 2009
March 23, 2009
March 25, 2009
April 7, 2009
April 24, 20090
May 1, 1009
May 8, 2009
May 29, 2009 (2)
June 2, 2009
June 5, 2009
June 8, 2009
July 15, 2009
July 22, 2009
July 23, 2009
July 24, 2009
July 28, 2009
August 18, 2009
August 26, 2009
September 17, 2009
September 25, 2009
September 30, 2009
October 8, 2009
October 9, 2009
October 15, 2009
October 23, 2009 (2)
November 18, 2009
January 8, 2010
January 28, 2010
February 2, 2010 (2)

Please note that your amendments dated January 28 and February 2, 2010 (pediatric information amendment only) were not reviewed for this action. You may incorporate applicable sections of these amendments by specific reference as part of your response to the deficiencies cited in this letter.

This new drug application provides for the use of Horizant (gabapentin enacarbil) for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

We have concluded that the application provides substantial evidence of effectiveness for Horizant (gabapentin enacarbil) as a treatment for patients with moderate to severe RLS. In particular, we have concluded that daily doses of 600 and 1200 mg are effective; however, we are not convinced that the 1200 mg dose provides additional benefit when compared to the 600 mg dose. The higher dose is associated with a greater frequency of adverse reactions and, for this reason, labeling should recommend a daily dose of 600 mg or lower, if the application is ultimately approved. The drug should be given at 5 PM.

Although we have not identified a clinical safety concern that would prevent approval of the 600 mg/day dose, the signal for pancreatic acinar cell tumors (adenoma, carcinoma) in the rat is of sufficient concern to preclude approval at this time.

Specifically, pancreatic acinar cell carcinoma was observed at a dose of 2000 mg/kg/day in male rats, and at a dose of 5000 mg/kg/day in both male and female rats. To put these findings into perspective, plasma exposure (area under the curve, AUC) at the lowest dose tested in male rats (500 mg/kg/day, the only dose that was *not* associated with tumors) is approximately 8-fold higher than the plasma AUC in humans receiving 600 mg/day. For female rats, tumors were not observed at 500 or 2000 mg/kg/day, and the corresponding margin at 2000 mg/kg/day is approximately 28-fold. Our view is that the 8-fold margin for the 600 mg daily dose, based on the finding of pancreatic carcinoma in the male rat, is unacceptably low. Furthermore, in the setting of carcinoma, hyperplasia and adenoma can reasonably be considered pre-cancerous lesions. We note an apparent increase in the incidence of pancreatic adenoma at a dose of 500 mg/kg/day in male rats. Because this was the lowest dose evaluated, a safety margin cannot be established. There was also an increase in acinar cell hyperplasia at the 2000 mg/kg/day dose in female rats, such that the safety margin for pre-cancerous hyperplasia in females is less than 28.

Even if we limit our concern to the occurrence of carcinoma, we view the exposure margin as unacceptable in the setting of RLS. We acknowledge that similar findings were known at the time of our approval of gabapentin, a closely related drug, for the treatment of refractory epilepsy. We believed at the time, and continue to believe, that the seriousness and severity of refractory epilepsy, and the benefit afforded these patients, justified the potential risk of pancreatic cancer. Although patients with RLS have very significant symptoms, it is our view that the seriousness of the condition is not sufficient to justify this risk.

We recognize that findings in laboratory animals are not necessarily translatable to risk in humans. Gabapentin products have been available for over 15 years, and they do not appear to be associated with a clinical signal for pancreatic cancer, based on an analysis of spontaneous reports in AERS. Although this may seem reassuring, we do not believe that the absence of a finding in analyses of spontaneous post-marketing reports can be reliably interpreted as evidence of absence of risk.

We are, of course, open to arguments that this concern should not prevent approval of this application. For example, were you able to demonstrate a mechanism of tumor formation in the rat that does not occur in humans, this would support the concept that the cancer signal is clinically irrelevant. At the moment, we are unaware of any such compelling mechanistic argument (you are undoubtedly aware that previous studies have not, to date, established any such mechanism; for example, the tumor has not been shown to be related to an increase in cholecystokinin). The language you have abstracted from the current gabapentin labeling describes the results of *in vitro* testing, suggesting that tumor formation may, in fact, result from a mechanism that is ubiquitous across species (increased mitogenic activity), thereby supporting the relevance of the signal for humans. These results notwithstanding, however, a search for a mechanism that is not at work in humans may be fruitful.

It is possible that a formal epidemiologic study could provide reassuring evidence that would dissociate the rat findings from humans, or, if the human risk could be adequately quantified, provide evidence that the risk is sufficiently low to be acceptable in patients with RLS.

Another potential route to approval may be a clinical study that demonstrates that Horizant is superior to other treatment(s) approved for RLS on an important clinical outcome.

Finally, as you know, even were the application to be approved, we have concluded that you should perform an additional clinical trial to determine the lowest effective dose of Horizant (the lack of dose-response among doses from 600 to 2400 mg/day suggests that doses lower than 600 mg may be equivalently effective). Given our concerns regarding cancer, identification of an effective Horizant dose significantly lower than 600 mg/day would provide a greater margin of safety, and might justify approval.

However, until and unless you can provide a compelling justification for approving a treatment that, in our view, poses a risk for a life threatening cancer for patients with RLS, we cannot approve this application.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

As described in our letter dated September 21, 2009, in accordance with section 505-1 of the FDCA, we have determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for Horizant (gabapentin enacarbil) to ensure that the benefits of the drug outweigh the risks, including the risks of suicidality and potential adverse effects on patients' ability to drive. The REMS, once approved, will create enforceable obligations.

We acknowledge receipt of your proposed REMS submitted on October 9, 2009.

We note that we sent you email correspondence on January 25, 2010 with comments pertaining to your proposed REMS. We will continue discussion of your proposed REMS and will notify you about the elements that will be required in the REMS, after your complete response to this action letter has been submitted. Our review of any additional data that you submit in response to this letter may necessitate changes to your proposed REMS.

On the first page of subsequent submissions related to the proposed REMS, prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22399 PROPOSED REMS-AMENDMENT

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

We also ask that your safety update specifically address the following comments:

1. Update the ISS with the data from the final study report from study XP055. List all patient exposures in both days and patient-years.

2. Please list all exposures by modal dose and duration for all flexible dose trials of XP13512.

3. Please include a more detailed accounting for patients who discontinued trial participation for the reasons listed as "withdrew consent" or "lost to follow-up" in all pivotal efficacy trials, long-term safety trials, and long-term maintenance of effect trials (study XP060).

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Beverly Conner, Regulatory Project Manager, at (301) 796-1171.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Deputy Director
Office of Drug Evaluation I
Center of Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLINE	SOLZIRA

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/s/

ELLIS F UNGER
02/17/2010