

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

22-115

**OTHER ACTION LETTER(s)**



NDA 22-115

SmithKlineBeecham Corporation  
d/b/a GlaxoSmithKline  
Attn: Elizabeth McConnell, Pharm.D.  
Associate Director, Regulatory Affairs,  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your new drug application (NDA) dated and received November 22, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal XR (lamotrigine) Extended-Release Tablets 25 mg, 50 mg, 100 mg, and 200mg.

We acknowledge receipt of your submissions dated:

|                   |                    |                 |
|-------------------|--------------------|-----------------|
| February 13, 2007 | March 19, 2007     | March 22, 2007  |
| April 12, 2007    | April 13, 2007     | April 20, 2007  |
| May 11, 2007      | June 5, 2007       | June 13, 2007   |
| June 19, 2007     | June 20, 2007      | July 18, 2007   |
| July 23, 2007     | July 25, 2007      | July 27, 2007   |
| August 01, 2007   | August 6, 2007     | August 10, 2007 |
| August 16, 2007   | August 17, 2007    | August 21, 2007 |
| August 27, 2007   | August 30, 2007    | August 31, 2007 |
| September 6, 2007 | September 10, 2007 |                 |

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following issues:

#### CLINICAL

Although we acknowledge that the results of Study LAM100034 (hereafter referred to as Study 34) clearly reach statistical significance overall, we are concerned about the marked discrepancy between the results in the U.S. and non-U.S. centers. Specifically, the median percentage change from baseline in seizure frequency (i.e. primary efficacy endpoint) for XR lamotrigine in foreign sites is 50 % vs 23% for placebo and the median percentage change from baseline in seizure frequency for XR lamotrigine in U.S. sites is 37 % vs 33% for placebo. The median treatment difference (according to the statistical analysis) was 3 % in the U.S. ( $p = 0.68$ ) and 26 % in foreign sites ( $p < 0.0001$ ), and the estimate of the treatment difference in the U.S. is substantially smaller

than in any other foreign country. Considering that approximately 36 % of randomized patients were studied in the U.S. (more than in any other foreign country), this difference is clearly not related to an inadequate sample size.

We have attempted to discover an explanation for this major discrepancy in effect of XR lamotrigine and to identify alternate analyses that might shed light on this difference. We have been unable to accomplish either.

For example, we have examined whether or not the imbalances in background AEDs between U.S. and non-U.S. patients (e.g., 9% of U.S. patients had regimens including valproate compared to 35% of non-U.S. patients; 57% of U.S. patients had regimens with EIAEDs without valproate compared to 47% of non-U.S. patients) might have resulted in a systematic decrease in lamotrigine levels in U.S. patients compared to non-U.S. patients. However, despite these differences, it appears that there is considerable overlap in the plasma levels of U.S. and non-U.S. patients. Nonetheless, you might be able to pursue this approach further (in this regard, we note that 33% of U.S. patients had "other" AED regimens compared to 18% of non-U.S. patients; perhaps it might be worthwhile pursuing this observation).

It is possible, however, that additional exposure-response analyses comparing data from all U.S. sites vs all foreign sites might be helpful.

In this regard, we note that the general approach that you have taken to describe the exposure-response for XR lamotrigine is reasonable, but the analyses that you have submitted do not allow us to decide whether there are differences in drug effects (and placebo effects) between U.S. and non-U.S./foreign sites. We recommend that you extend your Cmin-response analyses to investigate any potential U.S. and non-U.S. differences both in placebo and drug effects. It might be helpful to substantiate your findings with several sensitivity analyses using Study 34 study data for this purpose. Specifically, please conduct the exposure-response analyses for the following endpoints, in addition to any that you consider relevant:

- Seizure frequency rate % change from baseline during the double-blind phase (escalation and maintenance phases).
- Response rate (> or = 25%, > or = 50%).
- Test whether there are PK differences between U.S. and non-U.S. sites
- Please submit a detailed report showing relevant diagnostic plots, parameter estimates and their precision including mean, variance and SEs for all parameters and confidence intervals for slopes.

The geographic discrepancies in outcomes seen in Study 34 are particularly troubling in light of the results of your inspection of the 2 Korean sites. As you know, we have little experience with data from many of the countries included in this study (Russian Federation, Ukraine, India, Korea, Chile, Brazil, Argentina), and the findings of transcription and other errors from the Korean sites appear to raise serious questions about the reliability of not only the Korean data, but data from these other countries as well, especially given the fact that neither you nor we have performed audits of many of these sites (our inspection of the Korean sites is still pending). If the data from

these countries were not considered reliable, the lack of any effect seen in the U.S. centers would obviously take on even more importance.

In this regard, as we discussed in our telephone conversation of September 17, 2007, we ask that you submit the following information:

- We request that you inform us in detail about the nature and extent of all monitoring and/or inspections of study 34 at different periods including: 1) during the conduct of the study; 2) after completion of this study, but prior to NDA 22115 submission; and 3) after submission of NDA 22115.
- In particular, please specify and submit your Standard Operating Procedures (SOPs) for conducting not only monitoring but also inspections at study sites.
- Please specify which Study 34 sites were monitored or inspected at these different periods and specify the nature and extent of the monitoring including the percentage of verification of transcription of source data to CRFs for efficacy (especially data related to the primary efficacy endpoint), safety and PK data.
- Please specify the detailed findings/results of all inspections of any sites after submission of NDA 22115.
- Please submit the results of your planned reanalyses after corrections of the data from the 2 Korean sites as well as the detailed findings of the audit of these two sites.
- If you or any local operating companies (including any consultants/contractors) conducted any other inspections of Study 34 sites other than the 2 Korean sites, please describe the differences between these other inspections (e.g. nature and scope) vs the nature and scope of inspections at the 2 Korean sites.
- Please address our concerns, raised by the results of the Korean inspections, about the integrity of the data at the foreign sites that have not been audited/inspected.

We have requests for additional analyses of vital signs (VS). In study 34, you conducted all analyses assessing effects of treatment using the single set of VS data at the last visit immediately prior to randomization and initiation of treatment as the baseline comparator. In conducting these analyses, you did not include VS data from other, earlier pre-treatment visits (e.g. at least 2 more). We believe that including all pre-treatment VS in the calculation of the "baseline" value by averaging all pre-treatment VS data will potentially provide a better assessment of the baseline VS than a single set of VS data. A single set of VS data may not necessarily be a good reflection of the "true" or average VS for an individual patient for use as a comparator to multiple sets of VS measurements after treatment.

- We therefore request the following analyses be conducted for all VS data in Study 34 using all pre-treatment VS and averaging all these results for each parameter for each patient and comparing this "baseline" to all the post-treatment measurements at each visit.

- Please submit the analyses over time for: 1) mean absolute data for SBP, DBP, and pulse; 2) change from baseline for each VS parameter; 3) outlier results of potential clinical concern using the threshold criteria that we previously provided to you; and 4) a data listing of all patients with any outlier result. Outlier analyses should be presented as in the attached/appendix table (as previously requested from GSK).

**CMC**

1. Please remove the statement '(b) (4)' from the container label. We feel this is redundant since there is (b) (4) form.
2. Please provide updated drug product specifications, reflecting the revised dissolution specifications.

**CLINICAL PHARMACOLOGY**

Please adopt the following dissolution specifications:

**Table: Release Ranges for Dissolution Specifications for Lamotrigine Extended Release Tablets**

| 25 mg, 50 mg                     | 100 mg, 200 mg                   |
|----------------------------------|----------------------------------|
| Not more than (b) (4) at 2 hours | Not more than (b) (4) at 2 hours |
| (b) (4) at 7 hours               | (b) (4) at 5 hours               |
| Greater than (b) (4) at 15 hours | Greater than (b) (4) at 12 hours |

We have included draft labeling with this letter. However, of course whether or not the application can be approved on the basis of the results of Study 34 will depend upon you adequately addressing our concerns.

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 non-clinical and clinical studies 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 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 **showing these different datasets in the same table.**
  - 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 study discontinuation by incorporating the drop-outs from the newly completed studies and by **showing these different datasets in the same table**. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study 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 a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division discuss what steps need to be taken before the application may be approved.

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

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If you have any questions, call Teresa Wheelous, Sr. Regulatory Project Manager, at (301)796-1161.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D

Director

Division of Neurology Products

Center of Drug Evaluation and Research

Enclosure