CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-764/S-011
20-241/S-017

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-241/S-017
NDA 20-764/S-011

SmithKline Beecham Corporation
d/b/a GlaxoSmithKline
Attention: Eric B. Benson
Senior Director, Regulatory Affairs, Psychiatry
Five Moore Drive; P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Benson:

Please refer to your supplemental new drug applications (sNDAs) dated June 5, 2002, received June 6, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets.

We acknowledge receipt of your submission(s) dated:

October 4, 2002	November 13, 2002	December 12, 2002	February 4, 2003
October 8, 2002	November 14, 2002	December 20, 2002	February 19, 2003
October 18, 2002	November 15, 2002	January 3, 2003	February 24, 2003
October 28, 2002	November 22, 2002	January 20, 2003	March 3, 2003
November 1, 2002	December 2, 2002	January 29, 2003	March 7, 2003
November 11, 2002	December 11, 2002	February 3, 2003 (2)	March 21, 2003

We also acknowledge receipt of your submissions dated February 26, 2003 and March 27, 2003. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of these applications, as amended, and they are approvable. Before the applications may be approved, however, it will be necessary for you to address the following:

LABELING

1. Accompanying this letter (Enclosure) is the Agency's proposal for the labeling of lamotrigine for the maintenance treatment of Bipolar I Disorder to reduce the time to occurrence of mood episodes (mania, hypomania, depression, mixed episodes). We have used, as our base labeling, the labeling submitted in your March 7, 2003 amendment. Brackets [] embedded within the text that follows include comments and explanations concerning our proposed labeling.

   You must submit revised, draft labeling for lamotrigine as part of your response to this letter. In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes and identify which version of Lamictal labeling was used as the base document.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

2. Regarding Table 14 in the DOSAGE AND ADMINISTRATION section of labeling, we have asked that you provide the safety experience for patients in your clinical trials for whom the practice of doubling the Lamictal dose was followed after discontinuation of valproate. This request is similar to that sent to you in a February 25, 2003 electronic mail message. Your March 7, 2003 submission to these applications responded to our February 25, 2003 request, but did not include data to demonstrate safe use of the dosing recommendation. Therefore, we are reiterating our request that you provide data to demonstrate exactly what dosing practice was followed in these patients and data from these patients to support the safety of the dosing practice.

SAFETY UPDATE

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your sNDAs by submitting all safety information you now have regarding your new drugs. 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.
   - 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. 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.

PROMOTIONAL MATERIAL

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend these applications, notify us of your intent to file amendments, 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.

The drug products may not be legally marketed until you have been notified in writing that the applications are approved.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

58 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process