DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**NDA & sNDA APPROVAL**

NDA 022251
NDA 020241/S-036
NDA 020764/S-029

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

Dear Mr. Benson:

Please refer to your new drug application (NDA 022251) dated November 28, 2007, received November 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lamictal ODT (lamotrigine) Orally Disintegrating Tablets, 25mg, 50mg, 100mg, and 200mg.

We acknowledge receipt of your additional submissions to this NDA dated December 18, 2008, December 24, 2008, and March 26, 2009.

The December 24, 2008 submission constituted a complete response to our December 24, 2008 action letter.

This new drug application provides for a new immediate release formulation of lamotrigine.

We also refer to your supplemental new drug applications (NDA 020241/S-036 and 020764/S-029) dated December 17, 2008, received, December 17, 2008, submitted under 505(b) of the FDCA for Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets.

These supplemental new drug applications incorporate by reference the proposed labeling submitted to NDA 022251, Lamictal ODT Orally Disintegrating Tablets. Upon approval of NDA 022251, there will be a single package insert incorporating information from NDA 022251, NDA 020241, and NDA 020764.

We have completed our review of these applications. Accordingly, they are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **"SPL for approved NDA 22-251."**

## CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-251**" Approval of this submission by FDA is not required before the labeling is used.

We note that the carton and immediate container labels submitted on December 28, 2008 for all patient titration (starter) kits will require modification. We also note our agreement that use of these labels is permissible until the second printing as long as the intervening period of time does not exceed 6 months. Specifically, we note your agreement to replace in the labels the list of other drugs that may affect dosing of Lamictal ODT and to substitute a footnoted statement, "See prescribing information for other drugs that may affect dosing of Lamictal ODT."

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

**Adjunctive therapy of Partial Onset Seizures**
We are waiving the pediatric study requirement for ages birth up to 1 month for this application because the necessary studies are impossible or highly impracticable, as there are too few children in this age group with the disease to study.

This product is appropriately labeled for ages 1 month to 17 years for this indication. Therefore, no additional studies are needed in this pediatric group.

**Adjunctive therapy of Primary Generalized Tonic Clonic Seizures**

We are waiving the pediatric study requirement for ages birth up to 2 years for this application because the necessary studies are impossible or highly impracticable (there are too few children with the disease to study).

In addition, this product is appropriately labeled for use in ages 2 years up to 17 years for this indication. Therefore, no additional studies are needed in this pediatric group.

**Adjunctive therapy for Generalized Seizures of Lennox-Gastaut Syndrome**
Because this product for this indication has an orphan drug designation, you are exempt from this requirement.

**Conversion to Monotherapy in adults (≥16 years of age) with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED)**

We are waiving the pediatric study requirement for ages birth up to 16 years for this application because the necessary studies are impossible or highly impracticable (it is unethical to perform adequate placebo-controlled trials in monotherapy).

In addition, this product is appropriately labeled for use in ages 16 years and older for this indication. Therefore, no additional studies are needed in this pediatric group.

**Maintenance Treatment of Bipolar I Disorder**
We are waiving the pediatric study requirement for ages birth up to 10 years for this application because the necessary studies are impossible or highly impracticable (it is not possible to diagnose bipolar disorder reliably in this age group). Therefore, appropriate studies cannot be developed and carried out.

We are deferring submission of your pediatric study for ages 10 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1. Deferred pediatric study under PREA for the maintenance treatment of Bipolar I disorder in pediatric patients ages 10 to 17 years.

   Final Report Submission: July 31, 2013

Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated “Required Pediatric Assessment”.

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**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Lamictal (lamotrigine) Orally Disintegrating Tablets poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Lamictal (lamotrigine) Orally Disintegrating Tablets. FDA has determined that Lamictal (lamotrigine) Orally Disintegrating Tablets is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Lamictal (lamotrigine) Orally Disintegrating Tablet. FDA has also determined that Lamictal (lamotrigine) Orally Disintegrating Tablets is a product for which patient labeling could help prevent serious adverse effects related to the use of these products. . Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Lamictal (lamotrigine) Orally Disintegrating Tablet.

Your proposed REMS, submitted on March 26, 2009, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your March 26, 2009 submission.

Your assessment of the REMS should include an evaluation of:

a. A survey of patients' understanding of the serious risks of Lamictal (lamotrigine) Orally Disintegrating Tablets

b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)vii) [or 21 CFR 601.70] and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 22-251 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 22-251**
**PROPOSED REMS MODIFICATION**
**AND/OR**
**REMS ASSESSMENT [if included]**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

## LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jacqueline H. Ware, Pharm.D., Supervisory Regulatory Project Manager, at (301) 796-1160.

Sincerely,

*{See appended electronic signature page}*

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

Enclosures (FDA Approved Labeling Text, Medication Guide, and REMS)

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

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/s/

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Russell Katz

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