DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020711/S-045, S-046, S-047

SUPPLEMENT APPROVAL
REMS ASSESSMENT ACKNOWLEDGMENT
RELEASE REMS REQUIREMENT

SmithKline Beecham Corporation
d/b/a GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 22709

Attention: Jaisri Giridhar PhD, DABT, RAC
Manager, Global Regulatory Affairs

Dear Dr. Giridhar

Please refer to your following Supplemental New Drug Applications (sNDAs) and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ZYBAN (bupropion hydrochloride) sustained-release tablets:

Supplement Number	Submission Date	Receipt Date
S-045	December 22, 2015	December 22, 2015
S-046	April 7, 2016	April 7, 2016
S-047	January 27, 2017	January 27, 2017

We also refer to our December 16, 2016, Fulfillment of Postmarketing Requirement/Prior Approval Supplement Request Letter.

Finally, we acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated February 23, 2017. After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete and that the REMS was meeting its goals.

Supplement S-045 proposes a REMS modification to eliminate the requirements for the approved REMS for ZYBAN (bupropion hydrochloride).

Supplement S-046 proposes revisions to the **DRUG INTERACTIONS** section of the Package Insert to include information related to the interaction of ZYBAN and digoxin.

Supplement S-047 proposes revisions to the **BOXED WARNING, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, CLINICAL STUDIES,** and **PATIENT**

COUNSELING INFORMATION, and the Medication Guide as requested in our December 16, 2016, letter, to update the ZYBAN label based on the outcome of PMR 1630-1 "A Phase 4, Randomized, Double-Blind, Active and Placebo-Controlled, Multicenter Study Evaluating the Neuropsychiatric Safety and Efficacy of 12 Weeks Varenicline Tartrate 1 mg BID and Bupropion Hydrochloride 150 mg BID for Smoking Cessation in Subjects with and Without a History of Psychiatric Disorders."

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for ZYBAN (bupropion hydrochloride) was originally approved on February 26, 2010, and the most recent modification was approved on March 27, 2014. The REMS consists of a Medication Guide and a timetable for submission of assessment of the REMS. Your proposed modification to the REMS consists of removing the Medication Guide from the REMS and releasing the REMS requirements.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of ZYBAN (bupropion hydrochloride) outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Therefore, because the Medication Guide as an element of the REMS is no longer necessary to ensure the benefits of the drug outweigh the risks, a REMS is no longer required for ZYBAN (bupropion hydrochloride).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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 Mark Liberatore, PharmD, Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Sharon H. Hertz, MD
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling

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

/s/

JUDITH A RACOOSIN on behalf of SHARON H HERTZ
05/04/2017