DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021014/S-015, 19, 22, 24, 25, 27, and 28
NDA 021285/S-009, 13, 15, 18, 19, 20, and 22

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Kanan Solanki, M.S., RAC
Regional Brand Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Solanki:
Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trileptal® (oxcarbazepine) Tablets and Suspension in the table, below.

Application numbers (NDA 021014 is for Trileptal Tablets and NDA 021285 is for Trileptal Oral Suspension)	Type	Letter Date	Receipt date	Amendment dates	Provides for changes to the:
021014/S-015 021285/S-009	CBE	09/29/2005	10/3/2005		• Clinical Pharmacology - Special Populations - Hepatic Impairment subsection • Adverse Reactions - Postmarketing section to add Pancreatitis and/or lipase and/or amylase increase.
021014/S-019 021285/S-013	CBE	06/28/2006	06/29/2006	11/02/2007 11/03/2006 10/04/2006	• Precautions – -Multi-Organ Hypersensitivity subsection -Adds Hematologic Events subsection -Drug Interactions subsection to add cyclosporine to the list of drugs that have reduced plasma levels • Adverse Reactions - Postmarketing subsection- to add "Hemic and Lymphatic System - Bone marrow depression, agranulocytosis, aplastic anemia, pancytopenia, neutropenia"
021014/S-022 021285/S-015	CBE	05/09/2007	05/09/2007	11/02/2007	• Adverse Reactions - Postmarketing subsection- to add "Metabolism and Nutrition Disorders - Folic Acid Deficiency
021014/S-024 021285/S-018	PA	08/14/2008	08/14/2008	11/15/2010 12/15/2010	• Precautions - Pregnancy subsection and the Clinical Pharmacology - Special Populations - Pregnancy subsection – adds information regarding pharmacokinetics during pregnancy
021014/S-025 and 27		1/15/09	1/15/09	04/17/2009	Comprehensive Medication Guide and Risk

021285/S-019 and 20	PA			05/14/2010 09/09/2010 12/24/2010	Evaluation and Mitigation Strategy (REMS)
021014/S-028 021285/S-022	PA	6/30/09	6/30/09		Reformatting to comply with the Physician's Lableing Rule (PLR)

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide), and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any 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 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.

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

CARTON AND IMMEDIATE CONTAINER LABELS

Submit the final printed carton and container labels that are identical to the enclosed carton and immediate 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 these submissions "**Final Printed Container Labels for approved NDA 021014/S-025 and 27,and NDA 021285/S-019 and 020**" Approval of these submissions by FDA is not required before the labeling is used.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). The details of the REMS requirements were outlined in our REMS and safety labeling change notification letter dated December 16, 2008.

Since Trileptal® was approved on May 25, 2001, we have become aware of new safety information indicating an increased risk of suicidal thoughts and behavior with antiepileptic drugs (AEDs). An increased risk of suicidal thoughts and behavior was demonstrated in an FDA meta-analysis (dated May 23, 2008) of randomized, parallel-arm, placebo-controlled clinical trial data for 11 AEDs. In the meta-analysis, the odds ratio for suicidal behavior or ideation for all AEDs studied was 1.80 (95% CI: 1.24, 2.66); the estimated incidence of suicidal behavior or ideation was 0.43% among 27,863 drug-treated patients and 0.24% among 16,029 placebo-treated patients. This finding was generally consistent among drugs in the data analyzed. It was shared by drugs with varying mechanisms of action and was observed for all indications studied; this observation suggests that the risk applies to all AEDs regardless of indication of use. We consider this information to be "new safety information" as defined in section 505-1(b) of the FDCA.

Your proposed REMS, submitted on January 15, 2009, amended on September 9, 2010, and appended to this letter as amended, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. An evaluation of patients' understanding of the serious risks of Trileptal®

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), 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) 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 021014 and 021285 REMS ASSESSMENT**

- **NEW SUPPLEMENT FOR NDA 021014 and 021285**
  PROPOSED REMS MODIFICATION
  REMS ASSESSMENT

- **NEW SUPPLEMENT FOR (NEW INDICATION FOR USE)**
  FOR 021014 and 021285
  REMS ASSESSMENT
  PROPOSED REMS MODIFICATION (if included)

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

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

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

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. 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 http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

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:

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

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/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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 Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

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:
Content of Labeling
Container Labeling
REMS

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

/s/

RUSSELL G KATZ
03/03/2011