



NDA 22334/S-31

**SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation  
Attention: Joseph V. Posluszny, Ph.D.  
Executive Director, Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936

Dear Dr. Posluszny:

Please refer to your Supplemental New Drug Application (sNDA) dated November 20, 2014, received November 20, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afinitor (everolimus).

We acknowledge receipt of your amendments dated April 29, June 5, and September 9, 2015. We also refer to your submission of November 20, 2014, containing a postmarketing requirement (PMR) report for Study CRAD001C2485, entitled "Everolimus (RAD001) Therapy of Giant Cell Astrocytomas in Patients with Tuberous Sclerosis Complex," and to our September 18, 2015, letter stating that PMRs 1700-2 and 1700-4 have been fulfilled.

This "Prior Approval" supplemental new drug application revises the CLINICAL STUDIES, Subependymal Giant Cell Astrocytoma with Tuberous Sclerosis Complex (14.5) subsection of the package insert to provide five-year long term efficacy data results for Study CRAD001C2485.

The indication for the use of Afinitor for the treatment of patients with subependymal giant cell astrocytoma associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection was approved under the provisions of accelerated approval regulations (21 CFR 314.500) on October 29, 2010. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

We remind you of your postmarketing requirement specified in October 29, 2010, approval letter for NDA 22334/S-06. This requirement, along with required completion dates, is listed below.

**PMR 1700-1:**

Submit the final report (at least 4 years of follow-up) and datasets from M2301, a randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with everolimus versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

The timetable you submitted on October 26, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2011
Trial Completion:	September 2014
Final Report and Dataset Submission:	March 2015

### **APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is 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 text for the package insert, with the addition of any labeling changes in pending "Changes Being Effectuated" (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 includes 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).

## **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.

Because none of these criteria apply to your application, you are exempt from this requirement.

## **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, please call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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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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PATRICIA KEEGAN  
09/18/2015