



NDA 022334/S-009/S-010

**SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, New Jersey 07936-1080

Attention: Lincy Thomas, Pharm.D.  
Senior Associate Director

Dear Dr. Thomas:

Please refer to your Supplemental New Drug Applications (sNDAs) dated November 4 and December 23, 2010, received November 5 and December 27, 2010, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afinitor<sup>®</sup> (everolimus) Tablets, 2.5 mg, 5 mg, and 10 mg.

We acknowledge receipt of your amendments dated December 14 (2), 15, 20, 22 (2), 2010, January 6 (2), 17, 21 (2), 27, 31, February 2 (2), 3, 4 (2), 11 (2), 15, 17, 18, 23, March 2, 8, 9, 10, 15, 18, 24, 25, 30, April 4 (2), 25, and May 4, 2011.

“Prior Approval” supplemental new drug application S-009 provides for a new indication in patients with progressive neuroendocrine tumors of pancreatic origin (PNET) that are unresectable, locally advanced, or metastatic.

“Prior Approval” supplemental new drug application S-010 provides for the addition of safety information to the prescribing information for Afinitor<sup>®</sup> (everolimus). Specifically, the changes include the addition of language to the label regarding renal failure and urinary protein monitoring to the Warnings and Precautions section, and the addition of pulmonary embolism to the Adverse Reactions section.

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.

**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, text for the

patient package insert), 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 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.

### **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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for these indications has an orphan drug designation, you are exempt from this requirement.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Afinitor<sup>®</sup> (everolimus) Tablets were approved on March 30, 2009, we have become aware of two trials in which information on overall survival has not been reported. A decrease in overall survival of patients treated with Afinitor<sup>®</sup> (everolimus) Tablets would change the safety profile of this drug for this indication. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of a decrease in overall survival of patients treated with Afinitor<sup>®</sup> (everolimus) Tablets.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the signal of a serious risk of a decrease in overall survival of patients treated with Afinitor<sup>®</sup> (everolimus) Tablets.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1756-1** Submit the results of the final analysis of overall survival data from RAD001C2324 to further characterize the safety and efficacy profile of everolimus in pancreatic neuroendocrine tumors.

The timetable you submitted on May 4, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion: October 2013  
Final Report Submission: July 2014

- 1756-2** Submit the results of the final analysis of overall survival data from RAD001C2325 to further characterize the safety and efficacy profile of everolimus in carcinoid tumors.

The timetable you submitted on May 4, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion: October 2011  
Final Report Submission: July 2012

Submit all updates and final reports to this NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **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:

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>.

### **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 Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.  
Director  
Division of Drug Oncology Products  
Office of Oncology Drug 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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ROBERT L JUSTICE

05/05/2011