



NDA 022334/S-014/S-015

**SUPPLEMENT APPROVAL/  
FULFILLMENT OF POSTMARKETING  
REQUIREMENT AND COMMITMENT**

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

Attention: Lincy Thomas, Pharm.D.  
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Thomas:

Please refer to your Supplemental New Drug Applications (sNDAs) dated July 11 and 27, 2011, received July 11 and 27, 2011, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afinitor<sup>®</sup> (everolimus) tablets.

We acknowledge receipt of your amendments dated July 18, October 12 and November 23, 2011.

“Prior Approval” supplemental new drug application 014 provides for revisions to the package insert reflecting the final results from protocol C2240. This supplement was submitted in response to the following postmarketing commitment from the March 30, 2009, approval letter:

**610-2:** Submit the final, per-protocol overall survival analysis of protocol C2240 which was to be conducted 2 years after randomization of the last patient.

Protocol Submission: July 27, 2006  
Trial Start Date: December 6, 2006  
Final Report Submission: June 2010

“Prior Approval” supplemental new drug application 015 provides for revisions to the package insert based on results from a hepatic impairment study as well as a drug-drug interaction study with midazolam. This supplement was submitted in response to the following postmarketing requirement from the March 30, 2009, approval letter:

**610-1:** Conduct a trial in patients with severe hepatic impairment (Child-Pugh Class C). This trial need not be conducted in patients with cancer and a single dose evaluation will be appropriate. The protocol should be submitted prior to initiation for review and concurrence.

The timetable you submitted on March 3, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission: May 14, 2009  
Trial Start Date: October 14, 2009  
Final Report Submission: April 14, 2011

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.

In addition, we conclude that the above requirement and commitment were both fulfilled.

We remind you that there are postmarketing requirements listed in the October 29, 2010, and May 5, 2011, approval letters that are still open.

### **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).

### **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:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
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 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 Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

*{See appended electronic signature page}*

Amna Ibrahim, M.D.  
Deputy Director  
Division of Oncology Products 1  
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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AMNA IBRAHIM  
03/30/2012