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RESEARCH**

APPLICATION NUMBER:

22-334

APPROVAL LETTER



NDA 22-334

NDA APPROVAL

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

Attention: Sibylle R. Jennings, Ph.D.
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Jennings:

Please refer to your new drug application (NDA) dated June 27, 2008, received June 30, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afinitor[®] (everolimus) tablets 5 mg and 10 mg.

We acknowledge receipt of your submissions dated July 29, August 4, 20, 21 (2), 26, 29, September 5 (2), 9, 11, 25 (2), 29 (2), 30 (2), October 14, 17, 20, 21, 24, 28, 31, November 11, 19, 26, December 5, 10, 22, 2008, January 12, 20, 30, February 5, 10, 17, 18, 20, 23 (2), 25, 26, 27, March 3, 10, 11, 12, 20, 25, and 27, 2009.

This new drug application provides for the use of Afinitor[®] (everolimus) tablets for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

An expiration dating period of 24 months is granted when stored as recommended in the approved product labeling. You may extend the expiration dating based on accrual of real-time stability data and report this in an annual report for this NDA.

This application was not taken to a meeting of the Oncologic Drugs Advisory Committee (ODAC) because the application is based on a trial demonstrating a clinically and statistically significant improvement in progression-free survival with an acceptable benefit/risk ratio. Progression-free survival has previously been used as the basis for approval of drugs for the treatment of advanced renal cell carcinoma and the safety profile is similar to that of other drugs approved for this indication.

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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable since this disease does not occur in the pediatric population.

POSTMARKETING REQUIREMENTS UNDER 505 (o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize 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 (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Trial A2303 evaluated everolimus in patients with moderate hepatic impairment (Child Pugh Class B) and due to increases in everolimus exposure, a dose reduction is needed in these patients. No exposure data are available for patients with severe hepatic impairment and current labeling recommends that Afinitor® (everolimus) should not be used in these patients.

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 identify an unexpected serious risk of increased drug exposure when Afinitor® (everolimus) is administered to patients with severe hepatic impairment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the unexpected serious risk of increased drug exposure when Afinitor® (everolimus) is administered to patients with severe hepatic impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to complete the following postmarketing clinical trial:

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

Submit protocols to your IND 66,279, with a cross-reference letter to this NDA 22-334. Submit all final report(s) to your NDA. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing requirement 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.

POSTMARKETING COMMITMENTS

We remind you of your postmarketing commitments in your submission dated March 27, 2009. These commitments are listed below.

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

3. Develop a 2.5 mg dosage form (tablet) to allow for proper dose reductions when Afinitor[®] (everolimus) is co-administered with moderate CYP3A4 inhibitors. The 2.5 mg dosage form should be sufficiently distinguishable from the 5 mg and 10 mg tablets. Full chemistry, manufacturing and controls (CMC) information for the 2.5 mg dosage form including batch and stability data, updated labeling, and an updated environmental assessment should be submitted as a prior approval supplement.

Protocol Submission Date: May 14, 2009
Final Report Submission: January 14, 2010

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical trials number of patients entered into each trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**”, “**Postmarketing Commitment Final Report**”, or “**Postmarketing Commitment Correspondence**.”

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert and patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “SPL for approved NDA 22-334.”

CARTON AND IMMEDIATE CONTAINER LABELS

Submit 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 this submission “**Final Printed Carton and Container Labels for approved NDA 22-334**.” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and 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

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