DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22334/S-17 **ACCELERATED APPROVAL**

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, PharmD
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

Please refer to your Supplemental New Drug Application (sNDA) dated December 19. 2011, received December 19, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afinitor (everolimus) Tablets 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets.

We acknowledge receipt of your amendments dated February 24, March 29, and April 5, 13, 16, 19, 23, and 24, 2012.

This "Prior Approval" supplemental new drug application provides for the treatment of adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.

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.

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, Medication Guide), 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).

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. Therefore, you are required to conduct the following:

PMR #1892-1 To complete the ongoing clinical trial CRAD001M2302 entitled "A Randomized, Double-blind, Placebo-controlled Study of RAD001 in the Treatment of Angiomyolipoma in Patients with either Tuberous Sclerosis Complex (TSC) or Sporadic Lymphangioleiomyomatosis (LAM)" to further verify and describe the ultimate clinical outcomes of the duration of objective responses, incidence of nephrectomy and of renal embolization four years after randomization of the last patient in the study, as specified in the original protocol. You will submit the final comprehensive clinical study report, inclusive of all data collected in the clinical trial, as described in ICH E3.

The timetable you submitted on April 23, 2012, states you will conduct this trial according to the following schedule:

Final Protocol Submission:	June 10, 2010
Study/Trial Completion:	January 2015
Final Report Submission:	August 2015

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement**."

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 your request for orphan drug designation was granted, you are exempt from this requirement.

PROMOTIONAL MATERIALS

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

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

/s/

PATRICIA KEEGAN
04/26/2012

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFINITOR safely and effectively. See full prescribing information for AFINITOR.

AFINITOR (everolimus) tablets for oral administration
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------

Indications and Usage, Renal Angiomyolipoma with Tuberous Sclerosis Complex (1.3), Subependymal Giant Cell Astrocytoma (1.4), Dosage and Administration (2.1, 2.2), Warnings and Precautions (5.1, 5.3, 5.7) 04/2012
Dosage and Administration (2.2, 2.4), Warnings and Precautions (5.6, 5.7) 03/2012
Indications and Usage, Advanced Pancreatic Neuroendocrine Tumors (1.1), Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5) 05/2011

----------INDICATIONS AND USAGE----------

AFINITOR is a kinase inhibitor indicated for the treatment of:

- adults with progressive neuroendocrine tumors of pancreatic origin (PNET) that is unresectable, locally advanced or metastatic. The safety and effectiveness of AFINITOR in the treatment of patients with carcinoid tumors have not been established. (1.1)
- adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. (1.2)
- adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of AFINITOR in treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes. (1.3)
- adults and children ≥ 3 years of age with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TSC) who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of AFINITOR is based on an analysis of change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated. (1.4)

----------DOSAGE AND ADMINISTRATION----------

Advanced PNET, advanced RCC, or renal angiomyolipoma with TSC:

- 10 mg once daily with or without food. (2.1)
- For patients with hepatic impairment, reduce the AFINITOR dose. (2.2)
- If moderate inhibitors of CYP3A4 and/or P-glycoprotein (PgP) are required, reduce the AFINITOR dose to 2.5 mg once daily; if tolerated, consider increasing to 5 mg once daily. (2.2)
- If strong inducers of CYP3A4 are required, increase AFINITOR dose in 5 mg increments to a maximum of 20 mg once daily. (2.2)

SEGA:

- Initial dose based on body surface area with subsequent titration to attain trough concentrations of 5-10 ng/mL. (2.3)
- If moderate inhibitors of CYP3A4 and/or PgP are required, reduce the AFINITOR dose by approximately 50%. Subsequent dosing should be based on therapeutic drug monitoring (TDM). (2.4)
- If strong inducers of CYP3A4 are required, double the AFINITOR dose. Subsequent dosing should be based on TDM. (2.4)

Dose reduction or treatment interruption may be needed to manage adverse drug reactions. (2.2, 2.4)

----------DOSAGE FORMS AND STRENGTHS----------

2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets with no score (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients (4)

----------WARNINGS AND PRECAUTIONS----------

- Non-infectious pneumonitis: Monitor for clinical symptoms or radiological changes; fatal cases have occurred. Manage by dose reduction or discontinuation until symptoms resolve, and consider use of corticosteroids. (5.1)
- Infections: Increased risk of infections, some fatal. Monitor for signs and symptoms, and treat promptly. (5.2)
- Oral ulceration: Mouth ulcers, stomatitis, and oral mucositis are common. Management includes mouthwashes (without alcohol or peroxide) and topical treatments. (5.3)
- Renal failure: Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR. (5.4)
- Laboratory test alterations: Elevations of serum creatinine, blood glucose, and lipids may occur. Decreases in hemoglobin, neutrophils, and platelets may also occur. Monitor renal function, blood glucose, lipids, and hematologic parameters prior to treatment and periodically thereafter. (5.5)
- Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines. (5.8)
- Use in pregnancy: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus. (5.9, 8.1)

----------ADVERSE REACTIONS----------

Advanced PNET: Most common adverse reactions (incidence ≥ 30%) are stomatitis, rash, diarrhea, fatigue, edema, abdominal pain, nausea, fever, and headache. (6.1)
Advanced RCC: Most common adverse reactions (incidence ≥ 30%) are stomatitis, infections, asthenia, fatigue, cough, and diarrhea. (6.2)
Renal angiomyolipoma with TSC: Most common adverse reaction (incidence ≥ 30%) is stomatitis. (6.3)
SEGA: Most common adverse reactions (incidence ≥ 30%) are stomatitis, upper respiratory tract infection, sinusitis, otitis media, and pyrexia. (6.4)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong CYP3A4 inhibitors: Avoid concomitant use. (2.2, 2.4, 5.6, 7.1)
- Moderate CYP3A4 and/or PgP inhibitors: If combination is required, use caution and reduce dose of AFINITOR. (2.2, 2.4, 5.6, 7.1)
- Strong CYP3A4 inducers: Avoid concomitant use. If combination cannot be avoided, increase dose of AFINITOR. (2,2, 2.4, 5.6, 7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: Discontinue drug or nursing, taking into consideration the importance of drug to the mother. (8.3)
- Hepatic impairment: For advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with hepatic impairment, reduce AFINITOR dose. For SEGA patients with Child-Pugh class A or Child-Pugh class B hepatic impairment, adjustment to the starting dose may not be needed; however, subsequent dosing should be based on TDM. AFINITOR should not be used in SEGA patients with Child-Pugh class C hepatic impairment. (2.2, 2.4, 5.7, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 04/2012

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