DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 22-334

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman
Sr. Regulatory Manager
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Gutman:

Reference is made to your July 10, 2009 Proposed Pediatric Study Request for everolimus (RAD001, Afinitor®). Reference is also made to your amended Proposed Pediatric Study Request received September 3 and to your responses to the agency information request received October 28, 2009 and March 8, 2010.

Subependymal giant cell astrocytoma (SEGA) is a common manifestation of tuberous sclerosis, occurring in up to 20% of patients. It is the leading cause of death in children with tuberous sclerosis. SEGAs develop in the central nervous system in the subependymal layer of the lateral ventricle (often in the area of the caudate nucleus) and can protrude into the ventricle causing obstructive hydrocephalus. Case series have found the mean age at diagnosis to vary from 4.3 to 9.4 years. SEGAs are typically slow growing with annual growth rates of 20-30%, although rates of 200-300% are possible. Treatment involves total or subtotal resection. However, surgery remains a high risk procedure and incompletely resected tumors may recur after several years. Additional interventions are needed in this population.

To obtain needed pediatric information on everolimus (RAD001), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following studies:

Type of studies:

- **Study 1:** A non-randomized, open-label phase 2 study of everolimus for the treatment of patients with SEGA associated with tuberous sclerosis complex (TSC)
- **Study 2:** A randomized, double-blind, placebo-controlled phase 3 study of everolimus for the treatment of patients with SEGA associated with TSC

Indication to be studied: Treatment of patients with SEGA associated with TSC

Age group in which studies will be performed:

- **Study 1:** 3 years and older
- **Study 2:** Any age

Number of patients to be studied:

- **Study 1:** At least 28 patients. A minimum of 22 patients must be less than 18 years of age.
- **Study 2:** At least 99 patients. At least 74 patients from birth to less than 18 years.

Study endpoints:

- **Study 1:** The primary efficacy endpoint is reduction in SEGA tumor volume. The duration of response is also to be measured. Additional endpoints include safety and potential side effects, and the effect of everolimus on frequency of epileptiform events (in a subgroup of patients), and hydrocephalus.
- **Study 2:** The primary efficacy endpoint is SEGA response rate determined by the Independent Central Radiological Review of MRIs in the core treatment phase, obtained up to 6 months after the last patient is enrolled. Additional endpoints include absolute change from baseline in frequency of epileptiform events per 24 hours, time to SEGA progression, skin lesion response rate, change from baseline in angiogenesis markers, exposure of everolimus in treated patients, duration of SEGA response, time to SEGA response, and safety.

Drug information:

- **Study 1:**
  - *Dosage form:* 2.5 mg and 5 mg tablets
  - *Route of administration:* Oral
  - *Regimen:* An initial everolimus dose of 3 mg/m^2/day is to be administered as a daily or alternate day regimen, with dose titration to achieve a therapeutic pre-dose trough concentration range (5-15 ng/mL), subject to tolerability.
- **Study 2:**
  - *Dosage form:* 1 mg tablets
  - *Route of administration:* Oral
  - *Regimen:* An initial everolimus dose of 4.5mg/m^2 taken once daily, with dose titration to achieve a therapeutic pre-dose trough concentration range (5-15 ng/mL), subject to tolerability

Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under Section 505A(e)(1) of the Act, and 3) you have

not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with Section 505A(e)(2).

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

Drug specific safety concerns: The most common adverse events suspected as related to treatment with everolimus are hypogonadism, stomatitis, rash, anemia, fatigue, asthenia, diarrhea, anorexia, nausea, hypercholesterolemia, mucosal inflammation, vomiting, hypertriglyceridemia, cough, peripheral edema, dry skin, epistaxis, pruritus, and dyspnea. The most common Grade 3 or 4 adverse events suspected to be related to treatment are anemia, infections, hyperglycemia, stomatitis, fatigue, lymphopenia, hypercholesterolemia, pneumonitis, and elevated gamma-glutamyl transferase concentrations.

Statistical information, including power of studies and statistical assessments:

- **Study 1:** Provide summaries of demographic, safety, efficacy, and PK data. The sample size of 28, assuming a standard deviation of 1.33, would have at least 90% power to detect a mean reduction in SEGA volume, from baseline of at least $1cm^3$, based on a one-sided t-test with $\alpha = 0.025$. The non-parametric Wilcoxon signed rank test would also have approximately 90% power to detect a median reduction of $1cm^3$.
- **Study 2:** The primary analysis compares SEGA response rate between the two treatment arms using an exact Cochran-Mantel-Haenszel test. The patients will be randomized in a 2:1 ratio between everolimus and placebo. As there are no reported cases of tumor regression in patients with SEGA, the response rate on placebo is expected to be close to 0%. The SEGA response rate on everolimus is expected to be at least 20%. The sample size of 99 patients will provide at least 90% power to detect a difference of SEGA response rate, assuming a binomial distribution, between everolimus and placebo arms at a one-sided significance level of 0.025. Summaries of demographic, safety, and efficacy, data must be provided.
- **All studies:** Everolimus pharmacokinetics must be summarized using descriptive statistics. Relationships between dose, efficacy endpoints, safety endpoints and exposure must be

explored and presented for all patients. In addition, relationships between use of enzyme-inducing antiepileptic drugs and response and pharmacokinetic endpoints should be explored. If data from Study 1 and Study 2 allow, a PK-PD model should be developed to describe the relationships between dose and exposure and between exposure and efficacy and safety parameters.

Labeling that may result from the studies: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under Section 505A(j) of the Act, regardless of whether the studies demonstrate that everolimus is safe and effective, or whether such study results are inconclusive in the studied pediatric populations or subpopulations, the labeling must include information about the results of the studies.

Under Section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

Format and types of reports to be submitted: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under Section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before June 30, 2013. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request: Under Section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in Section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with Section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study reports. These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e., complete or partial response);
2. the status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, approvable, not approvable); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/cder/pediatric/index.htm**.**

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under Section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of Section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Paul Zimmerman, Regulatory Project Manager, at 301-796-2330.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22334	GI-1	NOVARTIS PHARMACEUTICALS CORP	AFFINITOR

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

/s/

RICHARD PAZDUR
04/01/2010