



NDA 203985

ACCELERATED APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Associate Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Gutman:

Please refer to your New Drug Application (NDA) dated February 29, 2012, received February 29, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Afinitor Disperz (everolimus tablets for oral suspension), 2mg, 3mg and 5mg.

We acknowledge receipt of your amendments dated March 2, April 3, April 12, (3) April 16, April 24, May 4, May 8, May 15, May 29, June 8, June 21, June 22, July 13, July 19, July 20, July 25, (2) July 26, August 9, August 13, and (3) August 27, August 28 and (2) August 29, 2012.

This NDA provides for the below indication for Afinitor Disperz (everolimus tablets for oral suspension):

Afinitor Disperz is indicated in pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. Effectiveness is based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume. Improvement in disease-related symptoms and overall survival in patients with SEGA and TSC has not been demonstrated.

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text and required patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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(1)] 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, text for the instructions for use). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels June 22, 2012, 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 (June 2008).” 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 203985.**” 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.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Vaishali Jarral
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2341
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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. You are required to conduct such studies with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval.

These requirements are the same as the accelerated approval requirements under NDA 22334/S-006, along with required completion dates, and are listed below.

PMR 1700-1:

Submit the final report (at least 4 years of follow-up) and datasets from M2301, a randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with everolimus versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). The timetable you submitted on October 26, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2011 (submitted)
Trial Completion:	September 2014
Final Report and Dataset Submission:	March 2015

PMR 1700-2:

Submit the long-term (at least 5 years) follow-up efficacy and safety data from C2485, a single-arm, single-institution, phase 2 trial evaluating treatment with everolimus in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). The timetable you submitted on October 26, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 2011 (submitted)
Trial Completion:	March 2014
Final Report and Dataset Submission:	November 2014

Submit final reports to this NDA as supplemental applications. For administrative purposes, all submissions relating to these postmarketing requirements must be clearly designated "**Subpart H Postmarketing Requirements.**"

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

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.

During the review of Afinitor® (everolimus) Tablets for the treatment of adult and pediatric patients, 3 years of age or older, with SEGA associated with TSC under NDA 22334/S-006, we became aware that the potential effect of Afinitor® (everolimus) on growth and development in the pediatric patient population was not adequately assessed because no long-term follow up data were available. This potential effect is also applicable to Afinitor Disperz (everolimus tablets for oral solution) for the same pediatric indication. Non-clinical data indicates that there exists dose-related delayed attainment of developmental landmarks including delayed eye opening, delayed reproductive development in males and females, and increased latency time during the learning and memory phases in juvenile rat toxicity studies. Furthermore, cases of low testosterone concentrations associated with high levels of follicle-stimulating hormone have been reported in the broader everolimus transplant program and no specific evaluation for the presence of hypogonadism has been performed. Therefore, 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 identify an unexpected serious risk of delayed attainment of developmental landmarks, delayed growth, and hypogonadism in the pediatric population.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be 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 identify an unexpected serious risk of delayed attainment of developmental landmarks, delayed growth, and hypogonadism in the pediatric population.

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

PMR 1700-3:

To evaluate the potential for serious risk of adverse long-term effects of Afinitor® (everolimus) on growth for pediatric patients, submit long-term follow-up data on patients enrolled on M2301, a randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with Afinitor® (everolimus) versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

All patients must be evaluated for growth and development milestones annually while still treated in the extension phase of M2301 (minimum of 4 years after randomization of the last patient). Evaluations must include the following: growth as measured by weight, height (measured with a stadiometer), height standard deviation scores (SDS), height velocity, height velocity SDS, age at thelarche (females), age at adrenarche (males), age at menarche (females), and Tanner Stage progression. Results of each evaluation must be documented.

Luteinizing and follicle stimulating hormones (LH, FSH), and testosterone levels in boys and LH, FSH and estradiol levels in girls must be measured in patients who have not developed secondary sexual characteristics by age 13 in girls and 14 in boys. Descriptive statistics (including mean and standard deviation values) of on-study data for growth velocity must be presented. Growth velocity during the trial should be compared with growth velocity at baseline (if pre-baseline data are available). Provide analyses of height and weight data that assess measures of central tendency and outlier analyses using height and weight z-scores.

The timetable you submitted on October 26, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2011 (submitted)
Trial Completion Date:	September 2014
Final Report and Dataset Submission:	March 2015

PMR 1700-4:

To evaluate the potential for serious risk of adverse long-term effects of Afinitor® (everolimus) on growth for pediatric patients, submit long-term follow-up data on patients enrolled on C2485, a single-arm, single-institution, phase 2 trial evaluating treatment with Afinitor® (everolimus) in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

All patients must be evaluated for growth and development milestones annually while still treated in the extension phase of C2485 (at least 5 years). Evaluations must include the following: growth as measured by weight, height (measured with a stadiometer), height standard deviation scores (SDS), height velocity, height velocity SDS, age at thelarche (females), age at adrenarche (males), age at menarche (females), and Tanner Stage progression. Luteinizing and follicle stimulating hormones (LH, FSH), and testosterone levels in boys and LH, FSH and estradiol levels in girls must be measured in patients who have not developed secondary sexual characteristics by age 13 in girls and 14 in boys. Descriptive statistics (including mean and standard deviation values) of on-study data for growth velocity must be presented. Growth velocity during the trial should be compared with growth velocity at baseline (if pre-baseline

data are available). Provide analyses of height and weight data that assess measures of central tendency and outlier analyses using height and weight z-scores.

The timetable you submitted on October 26, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 2011 (submitted)
Trial Completion Date:	March 2014
Final Report and Dataset Submission:	November 2014

Submit clinical protocols to your IND 66279, with a cross-reference letter to this NDA. Submit all final reports to your 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.

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
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We also remind you of your postmarketing commitments in your submissions dated August 13 and August 29, 2012:

PMC 1917-1:

To provide acceptable USP<671> Water Vapor Transmission Rate test (WVTR) results for the proposed commercial packaging system. Provide 3 months accelerated stability data on the first 3 commercial batches post approval when available, to demonstrate comparable stability with that of registration batches.

The timetable you submitted on August 13, 2012 stated that you will conduct this study and provide results according to the following schedule

Final Report Submission (USP <671> results):	November 2012
Three months accelerated stability data:	May 2013

PMC 1917-2:

To provide the dissolution method development report and prior approval supplement (including the revised dissolution method and information to support the dissolution acceptance criterion).

The timetable you submitted on August 29, 2012 stated that you will submit the above commitments according to the following schedule:

Dissolution Method Development Report Submission:	February 2013
Prior Approval Supplement Submission:	August 2013

Submit clinical protocols to IND 66279 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), 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 studies/trials, number of patients entered into each study/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**.”

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Vaishali Jarral, Regulatory Project Manager, at (301) 796-4248.

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(S):

Content of Labeling (including Patient Labeling and Instruction for Use)
Carton and Container 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
08/29/2012