



NDA 21560

NDA APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Mr. Ronald G. Van Valen
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

Please refer to your New Drug Application (NDA) dated December 19, 2002 and received December 20, 2002 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zortress (everolimus) Tablets, 0.25 mg, 0.5 mg, and 0.75 mg.

We acknowledge receipt of your submissions dated:

January 22, 2010	February 19, 2010	March 31, 2010	April 7, 2010
February 3, 2010	March 19, 2010	April 2, 2010	April 8, 2010
			April 13, 2010

The January 22, 2010 submission constituted a complete response to our December 23, 2009 action letter.

This new drug application provides for the use of Zortress (everolimus) Tablets for prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant.

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.

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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert and Medication Guide). For administrative purposes, please designate this submission, "**SPL for approved NDA 21560.**"

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 21560.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with labels that are not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

LABELING

Submit final printed labeling as soon as it is available, but no more than 30 days after it is printed. The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and Medication Guide), and must be in the “Drug Facts” format (21 CFR 201.66), where applicable.

The final printed labeling should be submitted 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 Labeling for approved NDA 21560.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with a package insert and Medication Guide that is not identical to the approved labeling text and Medication Guide in the required format may render the product misbranded and an unapproved new drug.

WEBSITE POSTING

We request that the labeling and Medication Guide approved today be available on your website within 10 days of receipt of this letter.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application for patients from birth to 16 years of age because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) 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 (section 505(o)(3)(A)).

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 assess signals of the serious risks of wound healing complications, hyperlipidemia, proteinuria, and graft thromboses.

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 signals of the serious risks of wound healing complications, hyperlipidemia, proteinuria, and graft thromboses.

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

1624-1 Trial RAD001A2309 “A 24-month, multicenter, randomized, open-label noninferiority study of efficacy and safety comparing concentration-controlled Certican™ in two doses (1.5 and 3.0 mg/day starting doses) with reduced Neoral® versus 1.44 g Myfortic® with standard dose Neoral in de novo renal transplant recipients” which contains the 24-month follow-up safety data on all patients enrolled in the trial.

Final protocol submission	Completed; trial is ongoing
Trial Completion Date:	August 18, 2009
Final Report Submission:	July 30, 2010

Submit the final report 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 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). The details of the REMS requirements were described in our complete response letter dated December 23, 2009.

Your proposed REMS, submitted on January 22, 2010, and amended on February 19, 2010, March 19, 2010, April 7, 2010, April 13, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

- a. A survey of healthcare providers' and patients' understanding of the serious risks of Zortress (everolimus).
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report

required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with one of the following wording selections applicable to the specific submission in bold capital letters at the top of the first page of the submission:

- **NDA 021560 REMS ASSESSMENT**
- **NEW SUPPLEMENT FOR NDA 021560
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**
- **NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021560
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of the REMS-related submissions.

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 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

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