DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21560/S-008

SUPPLEMENT 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 Supplemental New Drug Application (sNDA) dated and received April 6, 2012, 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 amendments dated May 10, 2012 and August 13, 2012.

The supplement provides for the following revisions to the Zortress® package insert:
(added text is underlined)

A. HIGHLIGHTS OF PRESCRIBING INFORMATION
DOSAGE AND ADMINISTRATION
• Starting oral dose of 0.75 mg twice daily. Adjust maintenance dose to achieve everolimus trough concentrations within the 3-8 ng/mL target range (using an LCMSMS assay method) (2.1, 2.2)

B. 2 DOSAGE AND ADMINISTRATION
2.2 Therapeutic Drug Monitoring - Everolimus
Routine everolimus whole blood therapeutic drug concentration monitoring is recommended for all patients using appropriate assay methodology. The recommended everolimus therapeutic range is 3 to 8 ng/mL. [*See Clinical Pharmacology (12.5)*] Careful attention should be made to clinical signs and symptoms, tissue biopsies, and laboratory parameters.

It is important to monitor everolimus blood concentrations, in patients with hepatic impairment, during concomitant administration of CYP3A4 inducers or inhibitors, when switching cyclosporine formulations and/or when cyclosporine dosing is reduced according to recommended target concentrations. [*See Clinical Pharmacology (12.5 and 12.6)*]

Optimally, dose adjustments of everolimus should be based on trough concentrations obtained 4 or 5 days after a previous dosing change. There is an interaction of cyclosporine on everolimus, and consequently, everolimus concentrations may decrease if cyclosporine exposure is reduced. [*See Drug Interactions (7.2)*]

The everolimus recommended therapeutic range of 3 to 8 ng/mL is based on an LCMSMS assay method. Currently in clinical practice, everolimus whole blood concentrations may be measured by chromatographic or immunoassay methodologies. Because the measured everolimus whole blood concentrations depend on the assay used, individual patient sample concentration values from different assays may not be interchangeable. Consideration of assay results must be made with knowledge of the specific assay used. Therefore, communication should be maintained with the laboratory performing the assay.

C. 6.3 Post Marketing Experience

Adverse reactions identified from the post-marketing use of the combination regimen of everolimus and cyclosporine that are not specific to any one transplant indication include angioedema [*See Warnings and Precautions (5.4)*], pancreatitis and pulmonary embolism. There have also been reports of male infertility with mTOR inhibitors including everolimus. [*See Warnings and Precautions (5.16)*].

D. 12.5 Everolimus Whole Blood Concentrations Observed in Kidney Transplant Patients

Based on exposure-efficacy and exposure-safety analyses of clinical trials and using an LCMSMS assay method, kidney transplant patients achieving everolimus whole blood trough concentrations ≥3.0 ng/mL have been found to have a lower incidence of treated biopsy-proven acute rejection compared with patients whose trough concentrations were below 3.0 ng/mL. Patients who attained everolimus trough concentrations within the range of 6 to 12 ng/mL had similar efficacy and more adverse events than patients who attained lower trough concentrations between 3 to 8 ng/mL. [*See Dosage and Administration (2.2)*]

E. 14.1 Prevention of Organ Rejection after Renal Transplantation

A 24-month, multi-national, open-label, randomized (1:1:1) trial was conducted comparing two concentration-controlled everolimus regimens of 1.5 mg per day starting dose (targeting 3 to 8 ng/mL using an LCMSMS assay method) and 3.0 mg per day starting dose (targeting 6 to 12 ng/mL using an LCMSMS assay method) with reduced doses of cyclosporine and corticosteroids, to 1.44 gm per day of mycophenolic acid with standard doses of cyclosporine and corticosteroids to 1.44 gm per day of mycophenolic acid with standard doses of cyclosporine and corticosteroids. The mean cyclosporine starting dose was 5.2, 5.0 and 5.7 mg/kg body weight/day in the everolimus 1.5 mg, 3.0 mg and in mycophenolic acid groups, respectively. The cyclosporine dose in the everolimus group was then adjusted to the blood trough concentration ranges indicated in

Table 3, whereas in the Myfortic group the target ranges were 200-300 ng/mL starting Day 5: 200-300 ng/mL, and 100-250 ng/mL from Month 2 to Month 12.

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, 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 via 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 with the revisions listed above and 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).

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, call Jacquelyn Smith, M.S., Senior Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D., MPH
Deputy Director for Safety
Division of Transplant and Ophthalmology Products
Office of Antimicrobial 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/

OZLEM A BELEN
10/02/2012