DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21560/S-018

SUPPLEMENT APPROVAL

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

Dear Mr. Van Valen:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 22, 2015, 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 also refer to our letter dated July 14, 2015, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for the class of mammalian target of rapamycin (m-TOR) inhibitors of which Zortress (everolimus) Tablets are members. This information pertains to the serious risk of pulmonary hypertension (PH), including pulmonary arterial hypertension (PAH), that suggest an association with the use of everolimus.

This supplemental new drug application provides for revisions to the labeling for Zortress (everolimus) Tablets, 0.25 mg, 0.5 mg, and 0.75 mg, consistent with our July 14, 2015 letter and agreed upon labeling revisions conducted through electronic mail correspondence dated October 19, 2015, as follows (additions are noted by underline):

The **5 WARNINGS AND PRECAUTIONS/5.10 Interstitial Lung Disease/Non-Infectious Pneumonitis** section is revised as follows:

Interstitial Lung Disease/Non-Infectious Pneumonitis

A diagnosis of interstitial lung disease (ILD) should be considered in patients presenting with symptoms consistent with infectious pneumonia but not responding to antibiotic therapy and in whom infectious, neoplastic and other non-drug causes have been ruled-out through appropriate investigations. Cases of ILD, implying lung intraparenchymal inflammation (pneumonitis) and/or fibrosis of non-infectious etiology, some reported with pulmonary hypertension (including pulmonary arterial hypertension [PAH]) as a secondary event, have occurred in patients receiving rapamycins and their derivatives,

including Zortress. Most cases generally resolve on drug interruption with or without glucocorticoid therapy. However, fatal cases have also occurred.

APPROVAL & LABELING

We have completed our review of these supplemental applications, 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), 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 that includes labeling changes 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).

PROMOTIONAL MATERIALS

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 Ms. June Germain, MS., Safety Regulatory Project Manager, at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, 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
11/05/2015