DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21083/S-058
NDA 21110/S-075

SUPPLEMENT APPROVAL

PF PRISM C.V.
c/o Pfizer, Inc.
Attention: Deneen Stewart, PhD
Director, Worldwide Safety and Regulatory
500 Arcola Road
Collegeville, PA 19426

Dear Dr. Stewart:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received August 14, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rapamune (sirolimus) Oral Solution and Rapamune (sirolimus) Tablets.

We acknowledge receipt of your amendments dated October 16, 2015.

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 Rapamune (sirolimus) Oral Solution and Rapamune (sirolimus) 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 sirolimus.

These supplemental new drug applications provide for revisions to the labeling for Rapamune (sirolimus) Oral Solution and Rapamune (sirolimus) Tablets, consistent with our July 14, 2015, letter and agreed upon labeling revisions through electronic mail correspondence dated October 2, 2015 as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~):

The **5 WARNINGS AND PRECAUTIONS/5.11 Interstitial Lung Disease** section is revised as follows:

Interstitial Lung Disease/Non-Infectious Pneumonitis

Cases of interstitial lung disease [ILD] (including pneumonitis, bronchiolitis obliterans organizing pneumonia [BOOP], and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the ILD was reported with pulmonary hypertension (including pulmonary arterial hypertension [PAH]) as a secondary event. In some cases, the ~~interstitial lung disease~~ ILD has resolved upon discontinuation or dose reduction of

Rapamune. The risk may be increased as the trough sirolimus concentration increases [see *Adverse Reactions (6.7)*].

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are 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 these supplemental applications, 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 thesesupplements, 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