DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21083/S061
NDA 21110/S080

SUPPLEMENT APPROVAL

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

Dear Dr. Stewart:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 29, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA #	**Supplement #**	**Product Description**
21083	S-061	Rapamune® (sirolimus) Oral Solution 1mg/mL
21110	S-080	Rapamune® (sirolimus) Tablet, 0.5 mg, 1 mg, and 2 mg.

These Prior Approval supplemental new drug applications provide for the following revisions to the package insert for these two products (additions are underlined text; deletions are in ~~strikethrough~~ text):

1. In the **6.4 Conversion from Calcineurin Inhibitors to Rapamune in Maintenance Renal Transplant Population**, a new paragraph is added at the end of the subsection to read:

   In a second study evaluating the safety and efficacy of conversion from tacrolimus to Rapamune 3 to 5 months post kidney transplant, a higher rate of adverse events, discontinuations due to adverse events, acute rejection, and new onset diabetes mellitus was observed following conversion to Rapamune. There was also no benefit with respect

to renal function and a greater incidence of proteinuria was observed after conversion to sirolimus [(*see Clinical Studies (14.4*)].

2. In the **12 CLINICAL PHARMACOLOGY/Drug-Drug Interactions**/Verapamil, the second sentence is revised as follows:

   The simultaneous oral administration of 2 mg daily of sirolimus oral solution and 180 mg q 12h of verapamil at steady state to ~~26~~ 25 healthy volunteers significantly affected the bioavailability of sirolimus and verapamil.

3. In the **14 CLINICAL STUDIES/14.4 Conversion from Calcineurin Inhibitors to Rapamune in maintenance Renal Transplant Patients**, the following two paragraphs are added at the end of the subsection:

   In an open-label, randomized, comparative, multicenter study where kidney transplant patients were either converted from tacrolimus to sirolimus 3 to 5 months post-transplant (sirolimus group) or remained on tacrolimus, there was no significant difference in renal function at 2 years post-transplant. Overall, 44/131 (33.6%) discontinued treatment in the sirolimus group versus 12/123 (9.8%) in the tacrolimus group. More patients reported adverse events 130/131 (99.2%) versus 112/123 (91.1%) and more patients reported discontinuations from the treatment due to adverse events 28/131 (21.4%) versus 4/123 (3.3%) in the sirolimus group compared to the tacrolimus group.

   The incidence of biopsy-confirmed acute rejection was higher for patients in the sirolimus group 11/131 (8.4%) compared to the tacrolimus group 2/123 (1.6%) through 2 years post-transplant. The rate of new-onset diabetes mellitus post-randomization, defined as 30 days or longer of continuous or at least 25 days non-stop (without gap) use of any diabetic treatment after randomization, a fasting glucose ≥126 mg/dL or a non-fasting glucose ≥200 mg/dL, was higher in the sirolimus group 15/82 (18.3%) compared to the tacrolimus group 4/72 (5.6%). A greater incidence of proteinuria, was seen in the sirolimus group 19/131 (14.5%) versus 2/123 (1.6%) in the tacrolimus group.

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, which is identical to the package insert submitted on May 21, 2018.

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 and Instructions for Use, 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 include 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).

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 Judit Milstein, Chief, Project Management Staff at 301-796-0763.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S): 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/

RENATA ALBRECHT
05/23/2018