DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21083/S-062
NDA 21110/S-081

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 December 15, 2017, and your amendment January 8, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number	Supplement Number	Name of Drug Product
NDA 21083	S-062	Rapamune® (sirolimus) Oral Solution, 1 mg/mL
NDA 21110	S-081	Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg

We also refer to our letter dated November 15, 2017, 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. This information pertains to the risk of embryo-fetal toxicities in animals, at exposures near or below those achieved in human transplant patients.

These supplemental new drug applications provides for revisions to the labeling for Rapamune. The agreed upon changes to the language included in our November 15, 2017, letter is as follows: (additions are noted by underline and deletions are noted by ~~strikethrough)~~

1. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION**: the **WARNINGS AND PRECAUTIONS** section, is revised to add a new bulleted title at the end of the list as follows:

    - Embryo-Fetal Toxicity (5.15, 8.1)

2. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION**: the **USE IN SPECIFIC POPULATIONS** section, is revised as follows:

   - Pregnancy: ~~Use only if the potential benefit outweights the potential risk to the embryo/fetus (8.1)~~ Based on animal data may cause fetal harm (5.15, 8.1)

3. In the **Full Prescribing Information: Contents**, the title "Embryo-Fetal Toxicity" section 5.15 has been added and all numbering and references have been updated throughout the labeling accordingly.

In the **FULL PRESCRIBING INFORMATION:**

4. In the **5 WARNINGS AND PRECAUTIONS** section**,** a new the subsection **5.15** titled "**Embryo-Fetal Toxicity"** is be added as follows:

   5.15 Embryo-Fetal Toxicity

   Based on animal studies and the mechanism of action *[see Clinical Pharmacology (12.1)]*, Rapamune may cause fetal harm when administered to a pregnant woman. In animal studies, mTOR inhibitors caused embryo-fetal toxicity when administered during the period of organogenesis at maternal exposures that were equal to or less than human exposures at the recommended lowest starting dose. Advise pregnant women of the potential risk to a fetus. Advise women of childbearing potential to avoid becoming pregnant and to use effective contraception while using Rapamune and for 12 weeks after ending treatment. *[see Use in Specific Populations (8.1)]*

5. The **8 USE IN SPECIFIC POPULATIONS/PREGNANCY** subsection is revised as follows**:**

   8.1 Pregnancy

   Pregnancy Category C: Sirolimus was embryo/fetotoxic in rats when given in doses approximately 0.2 to 0.5 the human doses (adjusted for body surface area). Embryo/fetotoxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). However, no teratogenesis was evident. In combination with cyclosporine, rats had increased embryo/feto mortality compared with sirolimus alone. There were no effects on rabbit development at a maternally toxic dosage approximately 0.3 to 0.8 times the human doses (adjusted for body surface area). There are no adequate and well- controlled studies in pregnant women. Effective contraception must be initiated before Rapamune therapy, during Rapamune therapy, and for 12 weeks after Rapamune therapy has been stopped. ~~Rapamune should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus.~~

6. The **MEDICATION GUIDE** is revised for consistency with the package insert, as well as administrative changes and/or editorial changes. See attached medication guide.

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 submitted on January 8, 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), 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).

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, Safety Regulatory Project Manager, at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MPH, MD
Deputy Director for Safety
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling, Medication guide

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
01/12/2018