DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50708/S-043
NDA 50709/S-036

SUPPLEMENT APPROVAL

Astellas Pharma US, Inc.
Attention: Mary Jo Pritza
Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Ms. Pritza:

Please refer to the following Supplemental New Drug Applications (sNDAs), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA):

Product Name	NDA Number	Supplement Number	Date of Submission	Date of Receipt
Prograf® (tacrolimus) Capsules, 0.5 mg, 1 mg, and 5 mg	50-708	S-043	March 14, 2013	March 15, 2013
Prograf® (tacrolimus) Injection, 5 mg/ml	50-709	S-036	March 14, 2013	March 15, 2013

We acknowledge receipt of your amendments dated August 29, 2013.

These "Prior Approval" supplemental new drug applications provide for the following revisions to the package insert of Prograf (deletions are shown in ~~strikethrough~~ font and additions are underlined):

5 WARNINGS AND PRECAUTIONS
5.13 Use with CYP3A4 Inhibitors and Inducers (b) (4) (b) (4) (b) (4) When coadministering Prograf with strong CYP3A4-inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong inducers (e.g., rifampin, rifabutin) (b) (4) (b) (4)-adjustments in the dosing regimen of (b) (4) Prograf and subsequent (b) (4) frequent monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions are recommended *[see Drug Interactions (7)]*.

(b) (4)

5.14 QT Prolongation

Prograf may prolong the QT/QTc interval and may cause Torsade de Pointes. Avoid Prograf in patients with congenital long QT prolongation syndrome. In patients with congestive heart failure, bradyarrhythmias, those taking certain antiarrhythmic medications or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia, consider obtaining electrocardiograms and monitoring electrolytes (magnesium, potassium, calcium) periodically during treatment.

When coadministering Prograf with other substrates and/or inhibitors of CYP3A4 that also have the potential to prolong the QT interval, a reduction in Prograf dose, frequent monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended. Use of Prograf with amiodarone has been reported to result in increased tacrolimus whole blood concentrations with or without concurrent QT prolongation [*see Drug Interactions (7)*].

5.18 Gastrointestinal Perforation

Gastrointestinal perforation has been reported in patients treated with tacrolimus; all reported cases were considered to be a complication of transplant surgery or accompanied by infection, diverticulum, or malignant neoplasm. As gastrointestinal perforation may be serious or life-threatening, appropriate medical/surgical management should be instituted promptly *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

- Gastrointestinal Perforation *[see Warnings and Precautions (5.18)]*

7 DRUG INTERACTIONS

Since tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes may increase tacrolimus whole blood concentrations. concentrations *[see Warnings and Precautions (5.13)* and *Clinical Pharmacology (12.3)]*. Dose adjustments may be needed along with frequent monitoring of tacrolimus whole blood trough concentrations when Prograf is administered with CYP3A inhibitors or inducers. In addition, patients should be monitored for adverse reactions including changes in renal function and QT prolongation [see *Warnings and Precautions (5.7) and (5.14)]*.

In addition, the cross references in the **HIGHLIGHTS of PRESCRIBING INFORMATION**, **FULL PRESCRIBING INFORMATION: CONTENTS*** and **FULL PRESCRIBING INFORMATION** have been revised to reflect the addition of the new subsections in the **5 WARNINGS AND PRECAUTIONS** as described above.

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.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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 NDAs, 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 applications, as well as annual reportable changes and annotate each change. To facilitate review of your submissions, 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 or by fax to 301-847-8444.

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}

Ozlem Belen, MD
Deputy Director for Safety
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/

OZLEM A BELEN
09/04/2013