DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50708/S-040
NDA 50709/S-033

SUPPLEMENT APPROVAL

Astellas Pharma
Attention: Eva Essig, PhD
Senior Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Dr. Essig:

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

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-040	January 18, 2012	January 19, 2012
Prograf® (tacrolimus) Injection, 5 mg/ml	50-709	S-033	January 18, 2012	January 19, 2012

We acknowledge receipt of your amendments dated May 10, May 30 and July 2, 2012.

These "Changes Being Effected in 30 days" supplemental new drug applications propose changes to the package insert to include information regarding drug interactions between tacrolimus and telaprevir or boceprevir as described below (added text is underlined, and deleted text is ~~strikethrough~~.)

1. The **HIGHLIGHTS OF PRESCRIBING INFORMATION** section has been revised as follows:

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, Use with CYP3A4 Inhibitors and Inducers Including Those that Prolong QT (5.13) 07/2012

2. The **FULL PRESCRIBING INFORMATION: CONTENTS** section has been revised as follows:

5 WARNINGS AND PRECAUTIONS
5.13 Use with ~~Strong~~ CYP3A Inhibitors and Inducers Including Those

That Prolong QT ~~of CYP3A~~

3. The **FULL PRESCRIBING INFORMATION,** Section 5.13 has been revised as follows:

5.13 Use with ~~Strong~~ CYP3A4 Inhibitors and Inducers Including Those That Prolong QT~~of CYP3A~~

Coadministration ~~Co-administration~~ with strong CYP3A4-inhibitors (e.g., telaprevir, boceprevir, ~~amiodarone,~~ ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong inducers (e.g., rifampin, rifabutin) is not recommended without adjustments in the dosing regimen of tacrolimus and subsequent close monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions [see *Drug Interactions (7)]*.

When coadministering tacrolimus with other substrates and/or inhibitors of CYP3A4 that also have the potential to prolong the QT interval, a reduction in tacrolimus dose, close monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended. Use of tacrolimus with amiodarone has been reported to result in increased tacrolimus whole blood concentrations with or without concurrent QT prolongation.

4. The **FULL PRESCRIBING INFORMATION**, Section 7.3 has been revised as follows:

7.3 Protease Inhibitors
Most protease inhibitors inhibit CYP3A enzymes and may increase tacrolimus whole blood concentrations. It is recommended to avoid concomitant use of tacrolimus with nelfinavir unless the benefits outweigh the risks *[see Clinical Pharmacology (12.3)]*. Whole blood concentrations of tacrolimus are markedly increased when coadministered with telaprevir or with boceprevir *[see Clinical Pharmacology (12.3)]*. Monitoring of tacrolimus whole blood concentrations and tacrolimus-associated ~~side effects~~ adverse reactions, and appropriate adjustments in the ~~dosage~~ dosing regimen ~~adjustments~~ of tacrolimus are recommended when tacrolimus and ~~other~~ protease inhibitors (e.g., ritonavir, telaprevir, boceprevir) are used concomitantly.

5. The **FULL PRESCRIBING INFORMATION**, Section 7.11 has been revised as follows:

7.11 Others
Bromocriptine, nefazodone, metoclopramide, danazol, ethinyl estradiol, amiodarone and methylprednisolone may inhibit CYP3A metabolism of tacrolimus and increase tacrolimus whole blood concentrations. Monitoring of blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are co-administered.

6. The **FULL PRESCRIBING INFORMATION**, Section 12.3 PHARMACOKINETICS/*Drug Interactions* has been revised as follows:

Drug Interactions
Frequent monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when concomitant use of the following drugs with tacrolimus is initiated or discontinued *[see Drug Interactions (7)]*.

Telaprevir: In a single dose study in 9 healthy volunteers, coadministration of tacrolimus (0.5 mg single dose) with telaprevir (750 mg three times daily for 13 days) increased the tacrolimus dose normalized C_{max} by 9.3-fold and AUC by 70-fold compared to tacrolimus alone *[see Drug Interactions (7.3)]*.

Boceprevir: In a single dose study in 12 subjects, coadministration of tacrolimus (0.5 mg single dose) with boceprevir (800 mg three times daily for 11 days) increased tacrolimus C_{max} by 9.9-fold and AUC by 17-fold compared to tacrolimus alone *[see Drug Interactions (7.3)]*.

7. The **Patient Information** section has been revised as follow:

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.
Especially tell your doctor if you take:
- cyclosporine (Gengraf®, Neoral®, and Sandimune®)
- sirolimus (Rapamune®)
- nelfinavir (Viracept®)
- telaprevir (Incivek™)
- boceprevir (Victrelis™)
- amiodarone (Cordarone™, Nexterone™, Pacerone™)

Ask your doctor or pharmacist if you are not sure if you take any of the medicines listed above.
PROGRAF may affect the way other medicines work, and other medicines may affect how PROGRAF works.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

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 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).

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 Hyun Son, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1600.

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:
Package Insert

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
07/05/2012