DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50708/S-038
NDA 50709/S-031

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-038	August 19, 2011	August 22, 2011
Prograf® (tacrolimus) Injection, 5 mg/ml	50-709	S-031	August 19, 2011	August 22, 2011

These "Changes Being Effected in 30 days" supplemental new drug applications propose changes to the ADVERSE REACTIONS section to add the events of "agranulocytosis" and "hemolytic anemia".

The submissions provide for the following revisions to the Prograf® package insert:
(added text is underlined, and deleted text is ~~strikethrough~~.)

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

   Revision: ~~7/2011~~2/2012

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

   16 HOW SUPPLIED/STORAGE AND HANDLING
   16.1 Prograf ~~Capsules~~ (tacrolimus ~~capsules~~) Capsules
   16.2 Prograf ~~Injection~~ (tacrolimus ~~injection~~) Injection

3. **6.2 Postmarketing Adverse Reactions/***Hemic/Lymphatic* section has been revised as follows:

   Hemic/Lymphatic
   Agranulocytosis, ~~D~~ddisseminated intravascular coagulation, hemolytic anemia, neutropenia, pancytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pure red cell aplasia *[see Warnings and Precautions (5.16)]*

4. **16 HOW SUPPLIED/STORAGE AND HANDLING**, **16.1** and **16.2** section titles have been revised as follows:

   16.1 Prograf ~~Capsules~~ (tacrolimus ~~capsules~~) Capsules
   16.2 Prograf ~~Injection~~ (tacrolimus ~~injection~~) Injection

5. The last section after **17.11 Immunizations** has been revised as follows:

   Rx only
   Marketed by:
   Astellas Pharma US, Inc.
   Deerfield, IL 60015-2548
   Revised: ~~July~~ February 201~~1~~2
   ~~09F003~~11G058-PRG

6. The Patient Information, **What is PROGRAF?** section, first paragraph has been revised as follows:

   PROGRAF is a prescription medicine used with other medicines to help prevent organ rejection in people who have had a kidney, liver, or heart transplant and PROGRAF is not for use with medicines called cyclosporines (Gengraf®, Neoral®, and Sandimune~~mue~~®).

7. The Patient Information, the following section has been revised as follows:

   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~~mue~~®)
   - sirolimus (Rapamune®)
   - nelfinavir (Viracept®)

8. The Patient Information, **What are the ingredients in PROGRAF?** section has been revised as follows:

What are the ingredients in PROGRAF?
Active ingredient: tacrolimus
Inactive ingredients: lactose monohydrate, hypromellose, croscarmellose sodium, ~~and~~ magnesium stearate, gelatin, titanium dioxide and ferric oxide.

9. The Patient Information, **Marketed by:** section has been revised as follows:

Marketed by:
Astellas Pharma US, Inc.
Deerfield, IL 60015-2548
Issued ~~July~~ February 201~~1~~2
~~09F003~~ 11G058-PRG-PI

We have completed our review of these supplemental applications. 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
02/06/2012