DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204096/S-002

SUPPLEMENT APPROVAL

Astellas Pharma US, Inc.
Attention: Glen Spears, PhD
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Spears:

Please refer to your Supplemental New Drug Application (sNDA) dated October 7, 2013, received October 8, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Astagraf XL (tacrolimus extended-release capsules).

This "Changes Being Effected" supplemental new drug application proposes changes to the **WARNINGS AND PRECAUTIONS** and the **DRUG INTERACTIONS** sections of the Package Insert, as well as various editorial revisions which relate to those changes.

APPROVAL

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text which is identical to the labeling text submitted on October 7, 2013.

LABELING REVISIONS

The approved revisions to the package insert are as follow (additions are noted with underline and deletions with ~~strikethrough~~):

In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, the following revisions have been made:

1. ----------**RECENT MAJOR CHANGES**----------
   Warnings and Precautions, Use with CYP3A4 Inhibitors and Inducers (5.14) 02/2014
   Warnings and Precautions, QT Prolongation (5.15) 02/2014
   Warnings and Precautions, Gastrointestinal Perforation (5.18) 02/2014

2. In the **FULL PRESCRIBING INFORMATION: CONTENTS**, two new subsections have been added to the **5 WARNINGS AND PRECAUTIONS** and subsections have been renumbered as follows:

5 WARNINGS AND PRECAUTIONS
5.14 Use with CYP3A Inhibitors and Inducers ~~Including Those That Prolong QT~~
5.15 QT Prolongation
5.16~~5~~ Immunizations
5.17~~6~~ Pure Red Cell Aplasia
5.18 Gastrointestinal Perforation

In the **FULL PRESCRIBING INFORMATION** section, the following revisions have been made:

3. The **5 WARNINGS AND PRECAUTIONS** section has been modified as follows:

5.14 Use with CYP3A Inhibitors and Inducers ~~Including Those That Prolong QT~~
When coadministering ASTAGRAF XL with strong CYP3A-inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong CYP3A inducers (e.g., rifampin, rifabutin), adjustments in the dosing regimen of ~~tacrolimus~~ ASTAGRAF XL and subsequent frequent monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions are recommended [*see Drug Interactions (7)*].

5.15 QT Prolongation
ASTAGRAF XL may prolong the QT/QTc interval and may cause Torsade de Pointes. Avoid ASTAGRAF XL in patients with congenital long QT 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 ASTAGRAF XL with other substrates and/or inhibitors of CYP3A that also have the potential to prolong the QT interval, a reduction in ~~tacrolimus~~ ASTAGRAF XL dose, frequent 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 *[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 (6.2)]*.

4. The **6 ADVERSE REACTIONS** section has been modified as follows:

   The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:
   - Lymphoma and Other Malignancies [*see Warnings and Precautions (5.2)*]
   - Serious Infections [*see Warnings and Precautions (5.3)*]
   - Polyoma Virus Infections [*see Warnings and Precautions (5.6)*]
   - Cytomegalovirus (CMV) Infections [*see Warnings and Precautions (5.7)*]
   - New Onset Diabetes after Transplant [*see Warnings and Precautions (5.8)*]
   - Nephrotoxicity [*see Warnings and Precautions (5.9)*]
   - Neurotoxicity [*see Warnings and Precautions (5.10)*]
   - Hyperkalemia [*see Warnings and Precautions (5.11)*]
   - Hypertension [*see Warnings and Precautions (5.12)*]
   - Pure Red Cell Aplasia [*see Warnings and Precautions (5.16~~7~~)*]
   - Gastrointestinal Perforation [*see Warnings and Precautions (5.18)*]

5. The **6.2 Postmarketing Experience** section is modified as follows:

   Gastrointestinal Disorders
   Dysphagia, gastrointestinal perforation [*see Warnings and Precautions (5.18)*], intestinal obstruction, peritonitis

6. The **7 DRUG INTERACTIONS** section is revised as follows:

   Since tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations [*see Warnings and Precautions (5.14), Clinical Pharmacology (12.3)*].
   Dose adjustments may be needed along with frequent monitoring of tacrolimus whole blood trough concentrations when ASTAGRAF XL 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 (5.9) and (5.15)*].

7. In the **12 CLINICAL PHARMACOLOGY** section, the paragraph below Table 6 is modified as follows:

   In *de novo* adult kidney transplant recipients, the tacrolimus systemic exposure, as assessed by ~~dose-adjusted~~ AUC24, for ASTAGRAF XL once daily on Day 1 post-transplant was 16% lower when compared with Prograf twice daily. By Day 3 post-

transplant, the ~~dose-adjusted~~ AUC24 was similar between the two formulations. On Day 14, the ~~dose-adjusted~~ AUC24 was 21% higher than Prograf, at comparable trough concentrations (C24).

8. In the **14 CLINICAL STUDIES** section, the sixth paragraph is modified as follows:

   Approximately 80% of ASTAGRAF XL patients maintained tacrolimus whole trough blood concentrations between 5 to 17 ng/mL during Months 1 through 2 and, then, between 4 to 12 ng/mL from Months 3 through 12.
   In Study 2, the protocol-specified target tacrolimus whole blood trough concentrations (Ctrough) were 10-15 ng/mL during the first month, 5-15 ng/mL from Month 2 to Month 6, and 5-10~~5~~ ng/mL thereafter. Approximately 80% of ASTAGRAF XL patients maintained tacrolimus whole trough blood concentrations between 6 to 20 ng/mL during Months 1 through 2 and, then between 6 to 14 ng/mL from Months 3 through 12.

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 includes 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 Ms. June Germain MS, Safety Regulatory Project Manager, at (301) 796-4024.

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: Content of Labeling
(Package Insert, 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
02/28/2014