DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-708/S-034
NDA 50-709/S-026

Astellas Pharma US, Inc.
Attention: Eva Essig, Ph.D.
Senior Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Dr. Essig:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA Number	Supplement Number	Date of Supplement	Date of Receipt
Prograf®(tacrolimus) Capsules, 0.5 mg, 1 mg, and 5 mg	50-708	S-034	December 23, 2008	December 24, 2008
Prograf® (tacrolimus) Injection, 5 mg/ml	50-709	S-026	December 23, 2008	December 24, 2008

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to the Prograf® Labeling:

Underlined text indicates addition. ~~Strikethrough~~ text indicates deletion.

1. Subheaders in the **WARNINGS** section have been added to facilitate readability and certain subsections are revised to add new safety information as follows. The text under these subheadings remains as currently approved, unless otherwise noted below:

   WARNINGS
   (see boxed **WARNINGS)**
   Post-Transplant Diabetes Mellitus

   Nephrotoxicity
   Prograf can cause **(b) (4)** nephrotoxicity, particularly when used in high doses.
   [The rest of the paragraph remains unchanged.]

   Hyperkalemia

   Neurotoxicity
   Prograf can cause neurotoxicity, particularly when used in high doses. [The rest of the first paragraph remains unchanged.]

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). Symptoms indicating PRES include headache, altered mental status, seizures, visual disturbances and hypertension. Diagnosis may be confirmed by radiological procedure. If PRES is suspected or diagnosed, blood pressure control should be maintained and immediate reduction of immunosuppression is advised. This syndrome is characterized by reversal of symptoms upon reduction or discontinuation of immunosuppression.

Malignancy and Lymphoproliferative Disorders

Latent Viral Infections
Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy which have been observed in patients receiving tacrolimus. These infections may lead to serious, including fatal, outcomes.

Prograf in Combination with MMF or Sirolimus
In one randomized, open-label, multi-center trial, 424 patients received Prograf (n=212) or cyclosporine (n=212) in combination with MMF 1 gram BID with basiliximab induction and corticosteroids. There was an imbalance in mortality at 12 months in those patients receiving Prograf/MMF (4.2%) compared to those receiving cyclosporine/MMF (2.4%), including cases attributed to overimmunosuppression. A safe and effective dosing regimen of MMF in combination with Prograf has not been established in kidney transplantation. (See **PRECAUTIONS/Other Drug Interactions**)

The use of full-dose Prograf with sirolimus (2 mg per day) in heart transplant recipients was associated with increased risk of wound healing complications, renal function impairment, and insulin dependent post transplant diabetes mellitus, and is not recommended (see **CLINICAL STUDIES**).

Anaphylactic Reactions

2. In the **PRECAUTIONS**/**Other Drug Interactions** subsection, a second paragraph has been added as follows:

   At a given MMF dose, mycophenolic acid (MPA) exposure is higher with Prograf co-administration than with cyclosporine co-administration due to the differences in the interruption of the enterohepatic recirculation of MPA. Clinicians should be aware that there is also a potential for increased MPA exposure after crossover from cyclosporine to tacrolimus in patients concomitantly receiving MMF or MPA (see **WARNINGS- Prograf in Combination with MMF or Sirolimus**).

3. The **ADVERSE REACTIONS/Urogenital** subsection has been revised as follows:

   Urogenital (see **WARNINGS**)
   Acute kidney failure, albuminuria, BK nephropathy, bladder spasm, cystitis, dysuria, hematuria, hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, oliguria, pyuria, toxic nephropathy, urge incontinence, urinary frequency, urinary incontinence, urinary retention, vaginitis

4. The **ADVERSE RECTIONS/Post Marketing/Nervous System** subsection has been revised as follows:

   Nervous System
   Carpal tunnel syndrome, cerebral infarction, hemiparesis, leukoencephalopathy, mental disorder, mutism, posterior reversible encephalopathy syndrome (PRES), progressive multifocal leukoencephalopathy (PML), quadriplegia, speech disorder, syncope

5. The **ADVERSE REACTIONS/Post Marketing/Respiratory** subsection has been revised as follows:

   Respiratory
   Acute respiratory distress syndrome, interstitial lung disease, lung infiltration, respiratory distress, respiratory failure

We completed our review of these applications. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant 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/

Renata Albrecht

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