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:

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

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 REACTIONS/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
 2/13/2009 12:33:30 PM