DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Makoto Nishimura, Ph.D.
President and CEO
Astellas Pharma US, Inc.
Three Parkway North
Deerfield, IL 60015

RE: NDA #50-708 and 50-709
Prograf (tacrolimus capsules and injection)
MACMIS ID #14259

WARNING LETTER

Dear Dr. Nishimura:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional journal advertisement (ad) for Prograf (tacrolimus capsules and injection) submitted by Astellas Pharma US, Inc. (Astellas) under cover of Form FDA 2253. The ad is false or misleading because it makes unsubstantiated superiority claims and minimizes the risks associated with Prograf. Thus, the journal ad misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §352(n) and FDA implementing regulations. See 21 C.F.R §§202.1(e)(5)(i) & (6)(ii).

Background

According to the Indications and Usage section of the FDA-approved product labeling that was in effect when the ad was disseminated (PI), Prograf is indicated for:

> [T]he prophylaxis of organ rejection in patients receiving allogeneic liver or kidney transplants. It is recommended that Prograf be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis, Prograf injection should be reserved for patients unable to take Prograf capsules orally.

The PI for Prograf contains the following boxed warning:

WARNING

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Prograf. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

The Warnings section of the PI contains additional risk information, some of which is in the form of bolded warnings. They include (in pertinent part):

Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of Prograf-treated kidney transplant patients without pretransplant history of diabetes mellitus in the Phase III study…. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM.

Insulin-dependent post-transplant diabetes mellitus was reported in 18% and 11% of Prograf-treated liver transplant patients and was reversible in 45% and 31% of these patients at one year post transplant, in the U.S. and European randomized studies, respectively…. Hyperglycemia was associated with the use of Prograf in 47% and 33% of liver transplant recipients in the U.S. and European randomized studies, respectively, and may require treatment (see **ADVERSE REACTIONS**).

Prograf can cause neurotoxicity and nephrotoxicity, particularly when used in high doses. Nephrotoxicity was reported in approximately 52% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving Prograf in the U.S. and European randomized trials, respectively (see **ADVERSE REACTIONS**). More overt nephrotoxicity is seen early after transplantation, characterized by increasing serum creatinine and a decrease in urine output. Patients with impaired renal function should be monitored closely as the dosage of Prograf may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Care should be taken in using tacrolimus with other nephrotoxic drugs. **In particular, to avoid excess nephrotoxicity, Prograf should not be used simultaneously with cyclosporine. Prograf or cyclosporine should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated Prograf or cyclosporine concentrations, dosing with the other drug usually should be further delayed.**

Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients and in 45% and 13% of liver transplant recipients treated with Prograf in the U.S. and European randomized trials, respectively, and may require treatment (see **ADVERSE REACTIONS**). **Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during Prograf therapy (**see **PRECAUTIONS).**

> Neurotoxicity, including tremor, headache, and other changes in motor function, mental status, and sensory function were reported in approximately 55% of liver transplant recipients in the two randomized studies. Tremor occurred more often in Prograf-treated kidney transplant patients (54%) compared to cyclosporine-treated patients. The incidence of other neurological events in kidney transplant was similar in the two treatment groups (see **ADVERSE REACTIONS**). Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment. Seizures have occurred in adult and pediatric patients receiving Prograf (see **ADVERSE REACTIONS**). Coma and delirium also have been associated with high plasma concentrations of tacrolimus.

The Precautions section of the PI states (in pertinent part):

> **General**
>
> Hypertension is a common adverse effect of Prograf therapy (see **ADVERSE REACTIONS**). Mild or moderate hypertension is more frequently reported than severe hypertension. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents.
>
> **Myocardial Hypertrophy**
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> Myocardial hypertrophy has been reported in association with the administration of Prograf, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. Hypertrophy has been observed in infants, children and adults.
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> In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving Prograf therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of Prograf should be considered.

In addition, the Clinical Studies section of the PI states (in pertinent part):

> **Kidney Transplantation**
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> Prograf-based immunosuppression following kidney transplantation was assessed in a Phase III randomized, multicenter, non-blinded, prospective study. There were 412 kidney transplant patients enrolled at 19 clinical sites in the United States. Study therapy was initiated when renal function was stable as indicated by a serum creatinine $\leq$ 4 mg/dL (median of 4 days after transplantation, range 1 to 14 days). Patients less than 6 years of age were excluded.
>
> There were 205 patients randomized to Prograf-based immunosuppression and 207 patients were randomized to cyclosporine-based immunosuppression. All patients received prophylactic induction therapy consisting of an antilymphocyte antibody preparation, corticosteroids and azathioprine. **Overall one year patient and graft survival was 96.1% and 89.6%, respectively, and was equivalent between treatment arms** (emphasis added).

> Because of the nature of the study design, comparisons of differences in secondary endpoints, such as incidence of acute rejection, refractory rejection or use of OKT3 for steroid-resistance rejection, could not be reliably made.

Unsubstantiated Superiority Claims

The ad presents the following claims regarding the superiority of Prograf to another therapy. The ad claims, "**STABLE RENAL FUNCTION** 5-year study… demonstrated minimal change in serum creatinine throughout Prograf treatment (median serum creatinine mg/dL: 1.4 Prograf vs 1.7 cyclosporine; *P*=0.0014)."[1] (emphasis original) The ad goes on to state, "**FAVORABLE CARDIOVASCULAR PROFILE** Significantly fewer Prograf-treated patients required antihypertensive (*P*=0.047) and antihyperlipidemia (*P*<0.001) medications than cyclosporine-treated patients in the 5-year trial."[1] (emphasis original) These claims are misleading because they suggest that Prograf is associated with fewer abnormalities of renal function, blood pressure, and lipids than cyclosporine when this has not been demonstrated by substantial evidence or substantial clinical experience.

The reference cited to support these claims does not constitute substantial evidence or substantial clinical experience. Serum creatinine and the use of antihypertensive and antihyperlipidemia medications were not primary efficacy endpoints in this study. Instead, these endpoints were reported as part of post hoc analyses of safety and adverse event data collection and are not sufficient to support the aforementioned claims.

The ad contains two headlines "**PRO-GRAFTED FOR LONG TERM SUCCESS**" and "**SUPERIOR REJECTION PREVENTION**" that when taken together conflict with language in your approved labeling. This presentation is misleading because it suggests that Prograf is better or more effective than cyclosporine in preventing organ rejection at one year and long term after renal transplantation when this has not been demonstrated. The primary endpoints of the study cited in the ad (and described in the Clinical Studies section of the PI) as support for these claims were overall one year patient and graft survival. Prograf was not superior to cyclosporine on these endpoints even though the study showed a statistically significant difference between Prograf and cyclosporine in regards to biopsy-confirmed acute rejection at one year. In such a case, a secondary endpoint such as biopsy-confirmed acute rejection at one year cannot support a conclusion of superiority. As stated in the Clinical Studies section of the PI, "Because of the nature of the study design, comparisons of differences in secondary endpoints, such as incidence of acute rejection, refractory rejection or use of OKT3 for steroid-resistant rejection, could not be reliably made."

Minimization of Risk

The ad also is false or misleading because it suggests that Prograf is safer than has been demonstrated by substantial evidence or substantial clinical experience. As discussed above, the ad includes the

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[1] Pirsch J, Miller J, Deierhoi MH, et al. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. *Transplantation.* 1997;63(7):977-983.
[2] Vincenti F, Jensik SC, Filo RS, et al. A long-term comparison for tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. *Transplantation.* 2002;73(5):775-782.

claim, "**FAVORABLE CARDIOVASCULAR PROFILE.**" (emphasis original) This claim misleadingly minimizes the cardiovascular risks associated with Prograf therapy. As stated in the Precautions section of the PI, "Hypertension is a **common** adverse event of Prograf therapy." (emphasis added) Hypertension is a common cardiovascular disease disorder and is a major risk factor for the development of heart disease, stroke, and kidney disease. In addition, the PI contains precautions regarding this and other cardiovascular events, such as myocardial hypertrophy.

Similarly, the claim, "**STABLE RENAL FUNCTION**" misleadingly minimizes the nephrotoxicity associated with Prograf therapy. Specifically, this claim suggests that patients taking Prograf will have stable renal (kidney) function. However, the PI includes Warnings regarding the potential for nephrotoxicity (toxicity to the kidney cells) with Prograf therapy. The Warnings section of the PI, states, "Nephrotoxicity was reported in approximately 52% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving Prograf in the U.S. and European randomized trials…." The PI further indicates, "More overt nephrotoxicity is seen early after transplantation, characterized by increasing serum creatinine and a decreased urine output. Patients with impaired renal function should be monitored closely as the dosage of Prograf may need to be reduced." This claim serves to minimize this important risk information.

We note that effectiveness claims are presented using large, bolded headers and with a significant amount of white space around them. However, the risk information is presented in the bottom half of the ad in a difficult to read font and typography. While we note that there is risk information regarding nephrotoxicity and hypertension in the lower part of the ad, this presentation is not sufficient to overcome the misleading suggestion that Prograf is safer than has been demonstrated, and results in a minimization of the risks.

Conclusion and Requested Action

The journal ad makes unsubstantiated implied superiority claims and minimizes the risks associated with Prograf in violation of the Act (21 U.S.C. §352(n)) and FDA implementing regulations. See 21 C.F.R §§202.1(e)(5)(i) & (6)(ii).

DDMAC requests that Astellas immediately cease the dissemination of violative promotional materials for Prograf such as those described above. Please submit a written response to this letter on or before September 15, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Prograf, such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at (301) 796-9877. In all future correspondence regarding this matter, please refer to MACMIS ID #14259 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Prograf comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams

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