DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Hideo Fukumoto
CEO
Fujisawa Healthcare, Inc.
Three Parkway North
Deerfield, IL 60015-2548

RE: NDA # 50-708, 50-709
Prograf® (tacrolimus capsules)
Prograf® (tacrolimus injection (for intravenous infusion only))
MACMIS ID # 12327

WARNING LETTER

Dear Mr. Fukumoto:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a journal advertisement (ad) for Prograf® (tacrolimus capsules and injection) by Fujisawa Healthcare, Inc. (Fujisawa) that appeared in the January 2004 issues of *Transplantation* and *The Journal of Heart and Lung Transplantation*. The ad violates section 502(n) of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 352(n)) in that it fails to include pertinent information about risks associated with Prograf in accordance with FDA implementing regulations (21 CFR 202.1(e)(3)(i)). In addition, the ad was not submitted on Form FDA 2253 at the time of initial dissemination, as required by 21 CFR 314.81(b)(3)(i). By failing to include sufficient qualifying information on risks, you have encouraged the potentially unsafe use of Prograf.

Background

The Indications and Usage section of the approved product labeling (PI) for Prograf states:

> Prograf is indicated for the 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:

> 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:

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 below (See Tables Below). The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these PTDM patients at one year and in 50% at two years post transplant. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM. . . . [tables omitted]

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 (See Table below). . . . [table omitted]

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**). . . . 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 . . . , 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 1iver 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.**

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…. 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. . . . .
>
> **Patients receiving Prograf injection should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If signs or symptoms of anaphylaxis occur, the infusion should be stopped. An aqueous solution of epinephrine should be available at the bedside as well as a source of oxygen**.

Brief Summary Requirement Violation

The main part of the ad contains various safety and effectiveness claims for Prograf. The headline, "I'm the luckiest kid alive!" is followed by: "With over 55,000 patients awaiting kidney transplantation, your choice of immunosuppression is vital. Prograf therapy provides effective protection against acute rejection and preserved long-term renal function. When resources are limited, your therapeutic decisions are more important than ever before." The main part of the ad also includes a reference to the brief summary of prescribing information and boxed warnings for Prograf on the adjacent page, and the following statement of risk information: "Common adverse reactions are nephrotoxicity, impaired glucose metabolism, neurotoxicity, gastrointestinal disturbances, hypertension, and infection."

This statement is not sufficient to provide the appropriate qualification or pertinent information for the claims made in the main part of the ad. Although FDA regulations (21 CFR 202.1(e)(3)(i)) provide for the "concise" presentation of such information, they do not authorize the use of terms that are themselves misleading to qualify claims of benefit. For example, information on the risk of increased susceptibility to infection, which is described in the boxed warning in the PI for Prograf, is necessary to qualify the claims of benefit appearing in the main part of the ad. The term "infection" does not sufficiently describe this risk. Similarly, information on the risk of insulin-dependent post-transplant diabetes mellitus, which is described in a bolded warning in the PI, is not sufficiently disclosed by "impaired glucose metabolism." The main part of the ad also fails to include necessary qualifying information concerning the risk of development of lymphoma, which also appears in the boxed warning in the PI for Prograf.

Failure to Submit Post-Marketing Reports

Your ad was not submitted on Form FDA 2253 at the time of initial dissemination, as required by the post-marketing reporting requirements (21 CFR 314.81(b)(3)(i)).

Conclusions and Requested Actions

The ad fails to present information on the risks associated with Prograf in compliance with 21 CFR 202.1(e)(3)(i). Accordingly, the ad violates section 502(n) of the Act, 21 USC 352(n), and misbrands Prograf. Moreover, the ad was not submitted to DDMAC at the time of initial dissemination, as required by 21 CFR 314.81(b)(3)(i).

DDMAC requests that Fujisawa 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 May 20, 2004, 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 information 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, HFD-42 Room 8B-45, 5600 Fishers Lane, Rockville MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12327 in addition to the NDA numbers. 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 described 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., MBA
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
5/7/04 02:34:08 PM