DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 50-708/S-021
NDA 50-709/S-013

Fujisawa Healthcare, Inc.
Attention: Linda M. Lieb, R.Ph., Ph.D.
Principle Scientist, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Dr. Lieb:

Please refer to your supplemental new drug applications dated May 5, 2003, received May 6, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prograf ® (tacrolimus) Capsules, 0.5 mg, 1mg, 5 mg and Prograf ® (tacrolimus) Injection, 5mg.

We acknowledge receipt of your submissions to each supplement dated November 13 and December 19, 2003, and January 23, March 26 and June 3, 2004.

Your submission of June 3, 2004 constituted a complete response to our November 6, 2003 action letter.

These supplemental new drug applications provide for the following revisions to the package insert (additions are double underlined and deletions are in ~~strikethrough~~):

1. PRECAUTIONS

- The following sentence was added to the end of the **Information for Patients** subsection:

  As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

- In the **"Drugs That May Alter Tacrolimus Concentrations"** subsection, the following revisions were made to the **"Drugs that May Increase Tacrolimus Blood Concentrations"** table:

  -voriconazole was added to the list of **Antifungal Agents**
  -magnesium-aluminum-hydroxide and chloramphenicol were added to the list of **Other Drugs**

- In the **"Drugs That May Alter Tacrolimus Concentrations"** subsection, the following revisions were made to the **"Drugs that May Decrease Tacrolimus Blood Concentrations"** table:

  -The subheading "~~**Antibioties**~~" are now called "**Antimicrobials**"
  -caspofungin was added to the list of **Antimicrobials**

-A new subheading was added called **"Other Drugs"** with sirolimus listed under that subheading

- In the **"Drugs That May Alter Tacrolimus Concentrations"** subsection, the following sentence was added concerning the drug interaction between tacrolimus and magnesium-aluminum-hydroxide:

  In a single-dose crossover study in healthy volunteers, co-administration of tacrolimus and magnesium-aluminum-hydroxide resulted in a 21% increase in the mean tacrolimus AUC and a 10% decrease in the mean tacrolimus C_{max} relative to tacrolimus administration alone.

- In the **"Drugs That May Alter Tacrolimus Concentrations"** subsection, the following paragraphs were revised/added:

  Interaction studies with drugs used in HIV therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir) or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are administered concomitantly with tacrolimus. Based on a clinical study of 5 liver transplant recipients, co-administration of tacrolimus with nelfinavir increased blood concentrations of tacrolimus significantly and, as a result, a reduction in the tacrolimus dose by an average of 16-fold was needed to maintain mean trough tacrolimus blood concentrations of 9.7 mg/mL. Thus, frequent monitoring of tacrolimus blood concentrations and appropriate dosage adjustment are essential when nelfinavir is used concomitantly. Tacrolimus may affect the pharmacokinetics of other drugs (e.g., phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided **(See DOSAGE AND ADMINISTRATION)**.

  Following co-administration of tacrolimus and sirolimus (2 or 5 mg/day) in stable renal transplant patients, mean tacrolimus AUC_{0-12} and C_{min} decreased approximately by 30% relative to tacrolimus alone. Mean tacrolimus AUC_{0-12} and C_{min} following co-administration of 1 mg/day of sirolimus decreased approximately 3% and 11%, respectively. The safety and efficacy of tacrolimus used in combination with sirolimus for the prevention of graft rejection has not been established and is not recommended.

2. **ADVERSE REACTIONS**

- In the **"Less Frequently Reported Adverse Reactions"** subsection the following paragraph was revised to read:

  ~~The overall safety profile of the Prograf-mycophenolate mofetil Phase IV study did not differ from the safety profile of the Phase III kidney study.~~
  There have been rare spontaneous reports of myocardial hypertrophy associated with clinically manifested ventricular dysfunction in patients receiving Prograf therapy (see **PRECAUTIONS-*Myocardial Hypertrophy***).

- The "**Post Marketing"** subsection was revised to read:

  The following have been reported: increased amylase including pancreatitis, hearing loss including deafness, leukoencephalopathy, thrombocytopenic purpura, hemolytic-uremic syndrome, acute renal failure, Stevens-Johnson syndrome, stomach ulcer, glycosuria, cardiac arrhythmia, QT prolongation, Torsades de Pointes and gastroenteritis.

  ~~There have been rare spontaneous reports of myocardial hypertrophy associated with clinically manifested ventricular dysfunction in patients receiving Prograf therapy (see **PRECAUTIONS-*Myocardial Hypertrophy***).~~

3. HOW SUPPLIED

- This section was revised to read:

  Prograf capsules (tacrolimus capsules)
  0.5 mg
  Oblong, light yellow, branded with red "0.5 mg" on the capsule cap and " 607" on the capsule body, supplied in ~~60 count~~ 100-count bottles (NDC 0469-0607-73) ~~and 10 blister cards of 10 capsules (NDC 0469-0607-10), containing the equivalent of 0.5 mg anhydrous tacrolimus~~.

  Prograf capsules (tacrolimus capsules)
  1 mg
  Oblong, white, branded with red "1 mg" on the capsule cap and 617
  on the capsule body, supplied in 100-count bottles
  (NDC 0469-0617-73)
  and 10 blister cards of 10 capsules (NDC 0469-0617-11), containing the equivalent of 1 mg anhydrous tacrolimus.

  Prograf capsules (tacrolimus capsules)
  5 mg
  Oblong, grayish/red, branded with white "5 mg" on the capsule cap and 657
  on the capsule body, supplied in 100-count bottles
  (NDC 0469-0657-73)
  and 10 blister cards of 10 capsules (NDC 0469-0657-11), containing the equivalent of 5 mg anhydrous tacrolimus.

  Made in Japan

  Store and Dispense
  Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

  Prograf injection (tacrolimus injection)
  5 mg (for IV infusion only)
  Supplied as a sterile solution in 1 mL ampules containing the equivalent of 5 mg of anhydrous tacrolimus per mL, in boxes of 10 ampules (NDC 0469-3016-01).

Made in Ireland

Store and Dispense
Store between 5°C and 25°C (41°F and 77°F).

Rx only
Manufactured for:
Fujisawa Healthcare, Inc.
Deerfield, IL 60015-2548

We have completed the review of these supplemental new drug applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted June 3, 2004).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: ***Providing Regulatory Submissions in Electronic Format - NDAs*** (January 1999) and ***Providing Regulatory Submissions in Electronic Format – Content of Labeling*** (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 50-708/S-021 and NDA 50-709/S-013." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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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