



NDA 50-708/S-025
NDA 50-709/S-018

Astellas Pharma US, Inc.
Attention: Donald E. Baker, J.D.
Senior Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Mr. Baker:

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-025	June 10, 2005	June 13, 2005
Prograf [®] (tacrolimus) Injection, 5 mg/ml	50-709	S-018	June 10, 2005	June 13, 2005

These “Changes Being Effected” supplemental new drug applications provide for the following revisions to the Prograf[®] Labeling:

- Addition of “Post Marketing Adverse Events” subsection to the ADVERSE REACTIONS section of the package insert.
- Addition of updated information to the “Less Frequently Reported Adverse Events” subsection of the ADVERSE REACTIONS section of the package insert.
- Update of the sponsor name change.

We completed our review of these applications and they are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text that includes the following changes:

Underlined text indicates addition. ~~Strikeout~~ text indicates deletion.

ADVERSE REACTIONS:

Less Frequently Reported Adverse Reactions

The following adverse events were reported in ~~the range of 3% to less than 15% incidence in either~~ liver or kidney transplant recipients who were treated with tacrolimus in the ~~Phase 3 comparative~~ clinical trials.

NERVOUS SYSTEM: (see **WARNINGS**) abnormal dreams, agitation, amnesia, anxiety, confusion, convulsion, crying, depression, dizziness, elevated mood, emotional liability, encephalopathy, haemorrhagic stroke, hallucinations, hypertonia, incoordination, monoparesis, myoclonus, nervous compression, nervousness, neuropathy, paralysis flaccid, psychomotor skills impaired, psychosis, quadriparesis, somnolence, thinking abnormal, writing impaired; **SPECIAL SENSES:** abnormal vision, amblyopia, ear pain, otitis media, tinnitus; **GASTROINTESTINAL:** anorexia, cholangitis, cholestatic jaundice, duodenitis, dyspepsia, dysphagia, esophagitis, flatulence, gastritis, gastroesophagitis, gastrointestinal hemorrhage, GGT increase, GI perforation, hepatitis, hepatitis granulomatous, ileus, increased appetite, jaundice, liver damage, liver function test abnormal, oesophagitis ulcerative, oral moniliasis, pancreatic pseudocyst, rectal disorder, stomatitis; **CARDIOVASCULAR:** angina pectoris, cardiac fibrillation, cardiopulmonary failure, chest pain, deep thrombophlebitis, abnormal ECG, echocardiogram abnormal, electrocardiogram QRS complex abnormal, electrocardiogram ST segment abnormal, heart rate decreased, hemorrhage, hypotension, postural hypotension, peripheral vascular disorder, phlebitis, tachycardia, thrombosis, vasodilation; **UROGENITAL:** (see **WARNINGS**) albuminuria, bladder spasm, cystitis, dysuria, hematuria, hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, oliguria, pyuria, toxic nephropathy, oliguria, urge incontinence, urinary frequency, urinary incontinence, urinary retention, vaginitis; **HEMIC/LYMPHATIC:** coagulation disorder, ecchymosis, haematocrit increased, haemoglobin abnormal, hypochromic anemia, leukocytosis, leucopenia, polycythemia, prothrombin decreased, serum iron decreased, thrombocytopenia; **MISCELLANEOUS:** abdomen enlarged, abscess, accidental injury, allergic reaction, cellulitis, chills, fall, feeling abnormal, flu syndrome, generalized edema, hernia, mobility decreased, peritonitis, photosensitivity reaction, sepsis, temperature intolerance, ulcer; **MUSCULOSKELETAL:** arthralgia, cramps, generalized spasm, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis; **RESPIRATORY:** asthma, bronchitis, cough increased, emphysema, hiccups, lung disorder, pneumothorax, pulmonary edema, pharyngitis, pneumonia, respiratory disorder, rhinitis, sinusitis, voice alteration; **SKIN:** acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, hirsutism, skin discoloration, skin disorder, skin ulcer, sweating.

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

Post Marketing

The paragraph for this section has been entirely deleted and the new information has been added.

~~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, Torsade de Pointes and gastroenteritis.~~

Post Marketing Adverse Events: The following adverse events have been reported from worldwide marketing experience with Prograf. Because these events are reported voluntarily from a population of uncertain size, are associated with concomitant diseases and multiple drug therapies and surgical procedures, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug.

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

Other Events Include:

CARDIOVASCULAR: atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest, electrocardiogram T wave abnormal, flushing, myocardial infarction, myocardial ischaemia, pericardial effusion, QT prolongation, Torsade de Pointes, venous thrombosis, deep limb, ventricular extrasystoles, ventricular fibrillation; GASTROINTESTINAL: bile duct stenosis, colitis, enterocolitis, gastroenteritis, gastroesophageal reflux disease, hepatic cytolysis, hepatic necrosis, hepatotoxicity, impaired gastric emptying, liver fatty, mouth ulceration, pancreatitis haemorrhagic, pancreatitis necrotizing, stomach ulcer, venoocclusive liver disease; HEMIC/LYMPHATIC: disseminated intravascular coagulation, neutropenia, pancytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura; METABOLIC/NUTRITIONAL: glycosuria, increased amylase including pancreatitis, weight decreased; MISCELLANEOUS: feeling hot and cold, felling jittery, hot flushes, multi-organ failure, primary graft dysfunction; NERVOUS SYSTEM: carpal tunnel syndrome, cerebral infarction, hemiparesis, leukoencephalopathy, mental disorder, mutism, quadriplegia, speech disorder, syncope; RESPIRATORY: acute respiratory distress syndrome, lung infiltration, respiratory distress, respiratory failure; SKIN: Stevens-Johnson syndrome, toxic epidermal necrolysis; SPECIAL SENSES: blindness, blindness cortical, hearing loss including deafness, photophobia; UROGENITAL: acute renal failure, cystitis haemorrhagic, hemolytic-uremic syndrome, micturition disorder.

The final printed labeling (FPL) must be identical, and include the revisions indicated above, to the submitted draft labeling (package insert submitted June 10, 2005). These revisions are terms of the approval of these applications.

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 is 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 supplement NDA 50-708/S-025 and NDA 50-709/S-018**”. Approval of these submissions by FDA is not required before the labeling is used.

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
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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

**This is a representation of an electronic record that was signed electronically and
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/s/

Renata Albrecht
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