DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-708/S-027
NDA 50-709/S-021

Astellas Pharma US, Inc.
Attention: Eva Essig, Ph.D.
Senior Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

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:

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-027	February 13, 2006	February 14, 2006
Prograf® (tacrolimus) Injection, 5 mg/ml	50-709	S-021	February 13, 2006	February 14, 2006

This application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated:

June 13, 2006
August 25, 2006
September 7, 2006 (2)
September 11, 2006
September 12, 2006
September 15, 2006
November 15, 2006
February 28, 2007
March 22, 2007 (2)
May 14, 2007
July 26, 2007
March 31, 2008
May 15, 2009

These supplemental applications propose to include information on the use of mycophenolate mofetil (MMF) with Prograf® for the prophylaxis of organ rejection in allogeneic kidney transplantation. We also refer to our approvable letter dated March 14, 2007, your submissions dated March 31, 2008, and to our correspondence dated July 22, 2008, indicating that your March 31, 2008 submission was an Incomplete Response to our approvable letter dated March 14, 2007.

Your submission dated May 15, 2009 constituted a complete response to our March 14, 2007 action letter.

The submissions provide for the following revisions to the Prograf® Package Insert:
(Underlined text indicates addition. ~~Strikethrough~~ text indicates deletion.)

1. The **CLINICAL STUDIES/Kidney Transplantation** subsection the first paragraph is revised as follows:

   Prograf/azathioprine
   Prograf-based immunosuppression in conjunction with azathioprine and corticosteroids following kidney transplantation was assessed in a Phase 3 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 ≤ 4 mg/dL (median of 4 days after transplantation, range 1 to 14 days). Patients less than 6 years of age were excluded.

2. In the **CLINICAL STUDIES/Kidney Transplantation** subsection, a new subsection titled "Prograf/mycophenolate mofetil (MMF)" is added as follows:

   Prograf/mycophenolate mofetil (MMF)
   Prograf-based immunosuppression in conjunction with MMF, corticosteroids, and induction has been studied. In a randomized, open-label, multi-center trial (Study 1), 1589 kidney transplant patients received Prograf (Group C, n=401), sirolimus (Group D, n=399), or one of two cyclosporine regimens (Group A, n=390 and Group B, n=399) in combination with MMF and corticosteroids; all patients, except those in one of the two cyclosporine groups, also received induction with daclizumab. The study was conducted outside the United States; the study population was 93% Caucasian. In this study, mortality at 12 months in patients receiving Prograf/MMF was similar (2.7%) compared to patients receiving cyclosporine/MMF (3.3% and 1.8%) or sirolimus/MMF (3.0%). Patients in the Prograf group exhibited higher estimated creatinine clearance rates (eCL_{cr}) using the Cockcroft-Gault formula (**Table 1**) and experienced fewer efficacy failures, defined as biopsy proven acute rejection (BPAR), graft loss, death, and/or lost to follow-up (**Table 2**) in comparison to each of the other three groups. Patients randomized to Prograf/MMF were more likely to develop diarrhea and diabetes after the transplantation and experienced similar rates of infections compared to patients randomized to either cyclosporine/MMF regimen (see **ADVERSE REACTIONS**).

Table 1: Estimated Creatinine Clearance at 12 Months in Study 1

Group	eCLcr [mL/min] at Month 12 [a]				
	N	MEAN	SD	MEDIAN	Treatment Difference with Group C (99.2% CI [b])
(A) CsA/MMF/CS	390	56.5	25.8	56.9	-8.6 (-13.7, -3.7)
(B) CsA/MMF/CS/Daclizumab	399	58.9	25.6	60.9	-6.2 (-11.2, -1.2)
(C) Tac/MMF/CS/Daclizumab	401	65.1	27.4	66.2	-
(D) Siro/MMF/CS/Daclizumab	399	56.2	27.4	57.3	-8.9 (-14.1, -3.9)
Total	1589	59.2	26.8	60.5	

Key: CsA=Cyclosporine, CS=Corticosteroids, Tac=Tacrolimus, Siro=Sirolimus

a) All death/graft loss (n=41, 27, 23 and 42 in Groups A, B, C and D) and patients whose last recorded creatinine values were prior to month 3 visit (n=10, 9, 7 and 9 in Groups A, B, C and D) were inputed with GFR of 10 mL/min; a subject's last observed creatinine value from month 3 on was used for the remainder of subjects with missing creatinine at month 12 (n=11, 12, 15 and 19 for Groups A, B, C and D). Weight was also imputed in the calculation of estimated GFR, if missing.

b) Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

Table 2: Incidence of BPAR, Graft Loss, Death or Loss to Follow-up at 12 Months in Study 1

	A N=390	B N=399	C N=401	D N=399
Overall Failure	141 (36.2%)	126 (31.6%)	82 (20.4%)	185 (46.4%)
Components of efficacy failure				
BPAR	113 (29.0%)	106 (26.6%)	60 (15.0%)	152 (38.1%)
Graft loss excluding death	28 (7.2%)	20 (5.0%)	12 (3.0%)	30 (7.5%)
Mortality	13 (3.3%)	7 (1.8%)	11 (2.7%)	12 (3.0%)
Lost to follow-up	5 (1.3%)	7 (1.8%)	5 (1.3%)	6 (1.5%)
Treatment Difference of efficacy failure compared to Group C (99.2% CI [a])	15.8% (7.1%, 24.3%)	11.2% (2.7%, 19.5%)	-	26.0% (17.2%, 34.7%)

Group A =CsA/MMF/CS, B =CsA/MMF/CS/Daclizumab, C=Tac/MMF/CS/Daclizumab, and D=Siro/MMF/CS/Daclizumab

a) Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

The protocol-specified target tacrolimus trough concentrations (C_{trough},Tac) were 3-7 ng/mL; however, the observed median $C_{troughs}$,Tac approximated 7 ng/mL throughout the 12 month study (**Table 3**).

Table 3: Tacrolimus Whole Blood Trough Concentrations (Study 1)

Time	Median (P10-P90 [a]) tacrolimus whole blood trough concentrations (ng/mL)
Day 30 (N=366)	6.9 (4.4 – 11.3)
Day 90 (N=351)	6.8 (4.1 – 10.7)
Day 180(N=355)	6.5 (4.0 – 9.6)
Day 365 (N=346)	6.5 (3.8 – 10.0)

a) Range of C_{trough}, Tac that excludes lowest 10% and highest 10% of C_{trough}, Tac

The protocol-specified target cyclosporine trough concentrations (C_{trough},CsA) for Group B were 50-100 ng/mL; however, the observed median $C_{troughs}$,CsA approximated 100 ng/mL throughout the 12 month study. The protocol-specified target $C_{troughs}$,CsA for Group A were 150-300 ng/mL for the first 3 months and 100-200 ng/mL from month 4 to month 12; the

observed median $C_{troughs}$, CsA approximated 225 ng/mL for the first 3 months and 140 ng/mL from month 4 to month 12.
While patients in all groups started MMF at 1g BID, the MMF dose was reduced to <2 g/day in 63% of patients in the tacrolimus treatment arm by month 12 (**Table 4**); approximately 50% of these MMF dose reductions were due to adverse events. By comparison, the MMF dose was reduced to <2 g/day in 49% and 45% of patients in the two cyclosporine arms (Group A and Group B, respectively), by month 12 and approximately 40% of MMF dose reductions were due to adverse events.

Table 4: MMF Dose Over Time in Prograf/MMF (Group C) (Study 1)

Time period (Days)	Time-averaged MMF dose (g/day) [a]		
	<2.0	2.0	>2.0
0-30 (N=364)	37%	60%	2%
0-90 (N=373)	47%	51%	2%
0-180 (N=377)	56%	42%	2%
0-365 (N=380)	63%	36%	1%

Time-averaged MMF dose = (total MMF dose)/(duration of treatment)

a) Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two g/day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

In a second randomized, open-label, multi-center trial (Study 2), 424 kidney transplant patients received Prograf (n=212) or cyclosporine (n=212) in combination with MMF 1 gram BID, basiliximab induction, and corticosteroids. In this study, the rate for the combined endpoint of biopsy proven acute rejection, graft failure, death, and/or lost to follow-up at 12 months in the Prograf/MMF group was similar to the rate in the cyclosporine/MMF group. There was, however, 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 (**Table 5**).

Table 5: Incidence of BPAR, Graft Loss, Death or Loss to Follow-up at 12 Months in Study 2

	Prograf/MMF (n=212)	Cyclosporine/MMF (n=212)
Overall Failure	32 (15.1%)	36 (17.0%)
Components of efficacy failure		
BPAR	16 (7.5%)	29 (13.7%)
Graft loss excluding death	6 (2.8%)	4 (1.9%)
Mortality	9 (4.2%)	5 (2.4%)
Lost to follow-up	4 (1.9%)	1 (0.5%)
Treatment Difference of efficacy failure compared		

to Prograf/MMF group (95% CI[a])	-	1.9% (-5.2%, 9.0%)

a) 95% confidence interval calculated using Fisher's Exact Test

The protocol-specified target tacrolimus whole blood trough concentrations (C_{trough},Tac) in Study 2 were 7-16 ng/mL for the first three months and 5-15 ng/mL thereafter. The observed median $C_{troughs}$,Tac approximated 10 ng/mL during the first three months and 8 ng/mL from month 4 to month 12 (**Table 6**).

Table 6: Tacrolimus Whole Blood Trough Concentrations (Study 2)

Time	Median (P10-P90[a]) tacrolimus whole blood trough concentrations (ng/mL)
Day 30 (N=174)	10.5 (6.3 – 16.8)
Day 60 (N=179)	9.2 (5.9 – 15.3)
Day 120 (N=176)	8.3 (4.6 – 13.3)
Day 180 (N=171)	7.8 (5.5 – 13.2)
Day 365 (N=178)	7.1 (4.2 – 12.4)

a) Range of C_{trough},Tac that excludes lowest 10% and highest 10% of C_{trough}, Tac

The protocol-specified target cyclosporine whole blood concentrations (C_{trough},CsA) were 125 to 400 ng/mL for the first three months, and 100 to 300 ng/mL thereafter. The observed median $C_{troughs,}$ CsA approximated 280 ng/mL during the first three months and 190 ng/mL from month 4 to month 12.
Patients in both groups started MMF at 1g BID. The MMF dose was reduced to <2 g/day by month 12 in 62% of patients in the Prograf/MMF group (**Table 7**) and in 47% of patients in the cyclosporine/MMF group. Approximately 63% and 55% of these MMF dose reductions were because of adverse events in the Prograf/MMF group and the cyclosporine/MMF group, respectively.

Table 7: MMF Dose Over Time in the Prograf/MMF group (Study 2)

Time period (Days)	Time-averaged MMF dose (g/day)[a]		
	<2.0	2.0	>2.0
0-30 (N=212)	25%	69%	6%
0-90 (N=212)	41%	53%	6%
0-180 (N=212)	52%	41%	7%
0-365 (N=212)	62%	34%	4%

Time-averaged MMF dose=(total MMF dose)/(duration of treatment)

a) Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two g/day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

3. The **INDICATIONS AND USAGE** section is revised as follows:

Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart 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. In heart and kidney transplant recipients, it is recommended that Prograf be used in conjunction with azathioprine or mycophenolate mofetil (MMF). The safety and efficacy of the use of Prograf with sirolimus has not been established (see **CLINICAL STUDIES**)

4. The **WARNINGS/Prograf in Combination with MMF or Sirolimus** subsection is revised as follows:

Prograf in Combination with ~~MMF or~~ Sirolimus

~~In one randomized, open-label, multi-center trial, 424 kidney transplant 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**).

5. The **PRECAUTIONS/Drug Interactions/Other Drug Interactions** subsection, the second paragraph is revised 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).~~

6. The **ADVERSE REACTIONS/Kidney Transplantation** subsection is revised as follows:

The most common adverse reactions reported were infection, tremor, hypertension, abnormal renal function, constipation, diarrhea, headache, abdominal pain and insomnia.
Adverse events that occurred in ≥ 15% of ~~Prograf treated~~ kidney transplant patients treated with Prograf in conjunction with azathioprine are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥ 15% OF ~~PROGRAF~~ PATIENTS TREATED ~~PATIENTS~~ WITH PROGRAF IN CONJUNCTION WITH AZATHIOPRINE

	Prograf (N=205)	**CBIR (N=207)**
Nervous System		

Tremor (see **WARNINGS**)	54%	34%
Headache (see **WARNINGS**)	44%	38%
Insomnia	32%	30%
Paresthesia	23%	16%
Dizziness	19%	16%
Gastrointestinal		
Diarrhea	44%	41%
Nausea	38%	36%
Constipation	35%	43%
Vomiting	29%	23%
Dyspepsia	28%	20%
Cardiovascular		
Hypertension (see **PRECAUTIONS**)	50%	52%
Chest pain	19%	13%
Urogenital		
Creatinine Increased (see **WARNINGS**)	45%	42%
Urinary Tract Infection	34%	35%
Metabolic and Nutritional		
Hypophosphatemia	49%	53%
Hypomagnesemia	34%	17%
Hyperlipemia	31%	38%
Hyperkalemia (see **WARNINGS**)	31%	32%
Diabetes Mellitus (see **WARNINGS**)	24%	9%
Hypokalemia	22%	25%
Hyperglycemia (see **WARNINGS**)	22%	16%
Edema	18%	19%
Hemic and Lymphatic		
Anemia	30%	24%
Leukopenia	15%	17%
Miscellaneous		
Infection	45%	49%
Peripheral Edema	36%	48%
Asthenia	34%	30%
Abdominal Pain	33%	31%
Pain	32%	30%
Fever	29%	29%
Back Pain	24%	20%

Respiratory System		
Dyspnea Cough Increased	22% 18%	18% 15%
Musculoskeletal		
Arthralgia	25%	24%
Skin		
Rash Pruritus	17% 15%	12% 7%

Adverse events that occurred in ≥ 10% of kidney transplant patients treated with Prograf in conjunction with MMF in Study 1* are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥ 10% OF PROGRAF-TREATED PATIENTS			
	Prograf (Group C)	**Cyclosporine (Group A)**	**Cyclosporine (Group B)**
	(N=403)	**(N=384)**	**(N=408)**
Anemia	17%	19%	17%
Leucopenia	13%	10%	10%
Diarrhea	25%	16%	13%
Edema peripheral	11%	12%	13%
Urinary tract infection	24%	28%	24%
Hyperlipidemia	10%	15%	13%
Hypertension (see **PRECAUTIONS**)	13%	14%	12%

*Study 1 was conducted entirely outside of the United States. Such studies often report a lower incidence of adverse events in comparison to US studies.

Adverse events that occurred in ≥15% of kidney transplant patients treated with Prograf in conjunction with MMF in Study 2 are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥ 15% OF PROGRAF-TREATED PATIENTS		
	Prograf	**Cyclosporine**
	(N=212)	**(N=212)**
Gastrointestinal Disorders		
Diarrhea	44%	26%
Nausea	39%	47%
Constipation	36%	41%
Vomiting	26%	25%
Dyspepsia	18%	15%
Injury, Poisoning, and Procedural		

Complications		
Post Procedural Pain	29%	27%
Incision Site Complication	28%	23%
Graft Dysfunction	24%	18%
	-	-
Metabolism and Nutrition Disorders	-	-
Hypomagnesemia	28%	22%
Hypophosphatemia	28%	21%
Hyperkalemia (see **WARNINGS**)	26%	19%
Hyperglycemia (see **WARNINGS**)	21%	15%
Hyperlipidemia	18%	25%
Hypokalemia	16%	18%
	-	-
Nervous System Disorders	-	-
Tremor	34%	20%
Headache	24%	25%
	-	-
Blood and Lymphatic System Disorders	-	-
Anemia	30%	28%
Leukopenia	16%	12%
	-	-
Miscellaneous	-	-
Edema Peripheral	35%	46%
Hypertension (see **PRECAUTIONS**)	32%	35%
Insomnia	30%	21%
Urinary Tract Infection	26%	22%
Blood creatinine increased	23%	23%

7. The **DOSAGE AND ADMINISTRATION/Prograf capsules (tacrolimus capsules)** subsection table is revised as follows:

Summary of Initial Oral Dosage Recommendations and ~~Typical~~ Observed Whole Blood Trough Concentrations

Patient Population	**Recommended Initial Oral Dosage**[a]	**~~Typical~~ Observed Whole Blood Trough Concentrations**
Adult kidney transplant patients In combination with azathioprine	0.2 mg/kg/day 0.1 mg/kg/day	month 1-3: 7-20 ng/mL month 4-12: 5-15 ng/mL month 1-12: 4-11 ng/mL

In combination with MMF/IL-2 receptor antagonist [b]		
Adult liver transplant patients	0.10-0.15 mg/kg/day	month 1-12: 5-20 ng/mL
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	month 1-12: 5-20 ng/mL
Adult heart transplant patients	0.075 mg/kg/day	month 1-3: 10-20 ng/mL month ≥4: 5-15 ng/mL

a) Note : two divided doses, q12h

b) In a second smaller study, the initial dose of tacrolimus was 0.15-0.2 mg/kg/day and observed tacrolimus concentrations were 6-16 ng/mL during month 1-3 and 5-12 ng/mL during month 4-12 (see **CLINICAL STUDIES**).

8. The **DOSAGE AND ADMINISTRATION/Kidney Transplantation** subsection is revised as follows:

The recommended starting oral dose of Prograf ~~is 0.2 mg/kg/day~~(administered every 12 hours in two divided doses) is 0.2 mg/kg/day when used in combination with azathioprine or 0.1 mg/kg/day when used in combination with MMF and IL-2 receptor antagonist (see **CLINICAL STUDIES**). The initial dose of Prograf may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered (as indicated for example by a serum creatinine ≤ 4 mg/dL). Black patients may require higher doses to achieve comparable blood concentrations. Dosage and typical tacrolimus whole blood trough concentrations are shown in the table above; blood concentration details are described in **Blood Concentration Monitoring**: ***Kidney Transplantation*** below.

9. The **DOSAGE AND ADMINISTRATION/Blood Concentration: Kidney Transplantation** subsection is revised as follows:

Data from ~~the~~ a Phase 3 study of Prograf in conjunction with azathioprine indicate that trough concentrations of tacrolimus in whole blood, as measured by IMx® were most variable during the first week of dosing. During the first three months of that trial, 80% of the patients maintained trough concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through 1 year.

In a separate clinical trial of Prograf in conjunction with MMF and daclizumab, approximately 80% of patients maintained tacrolimus whole blood concentrations between 4-11 ng/mL through 1 year post-transplant.

In another clinical trial of Prograf in conjunction with MMF and basiliximab, approximately 80% of patients maintained tacrolimus whole trough blood concentrations between 6-16 ng/mL during month 1-3 and, then, between 5-12 ng/mL from month 4 through 1 year.

The relative ~~risk~~ risks of toxicity ~~is increased with higher~~and efficacy failure are related to tacrolimus whole blood trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity and efficacy 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, submitted May 15, 2009.

LETTERS TO HEALTH CARE PROFESSIONALS

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

REPORTING REQUIREMENTS

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

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