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News Release

For Immediate Release

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ASTELLAS RECEIVES FDA APPROVAL FOR USE OF PROGRAF® (TACROLIMUS) IN CONJUNCTION WITH MYCOPHENOLATE MOFETIL (MMF) IN KIDNEY TRANSPLANT RECIPIENTS

Deerfield, IL (May 28, 2009) – The Food and Drug Administration (FDA) has granted Astellas Pharma US, Inc. approval for the use of Prograf® (tacrolimus) in conjunction with mycophenolate mofetil (MMF) for the prevention of organ rejection in kidney transplant recipients. Prograf is a cornerstone therapy for preventing transplant rejection in liver, kidney and heart transplant recipients. The approval came on May 19, 2009 in response to a Supplemental New Drug Application (sNDA) originally submitted in 2006. Prograf's combination use with MMF for heart transplant recipients was approved by the FDA in March 2006.

"Prograf + MMF has been an accepted and successful immunosuppressant regimen for the transplant community for more than 10 years," said Flavio Vincenti, M.D., Professor of Clinical Medicine, University of California, San Francisco, Division of Nephrology. "This FDA approval recognizes the most commonly used regimen of transplant centers and reinforces the importance of this combination therapy in the treatment of kidney and heart transplant recipients."

"The FDA approval of Prograf + MMF for use in kidney transplant patients is a milestone for the transplant community as a whole, but most of all it is a milestone for all the patients in the U.S. as it will facilitate the development of new immunosuppressive drugs," said Goran B. Klintmalm, M.D., Ph.D., Chairman and Chief of the Baylor Regional Transplant Institute, Dallas/Fort Worth. "It allows us to use the current standard of care as the control arm in future clinical studies to further advance the timely clinical development of new agents in transplantation."

Prograf was initially approved by the FDA in 1994 and is currently used in the majority of patients following kidney, liver and heart transplants. According to United Network for Organ Sharing (UNOS), in 2007, 79.3% of kidney transplant recipients were discharged with a Prograf + MMF medication regimen.

The Clinical Studies

The FDA's approval of Prograf + MMF for use in kidney transplant recipients was based on the review of two clinical studies involving approximately 2,000 kidney transplant recipients. A phase III, multi-center, open-label clinical trial was conducted where 424 kidney transplant recipients received Prograf or cyclosporine in combination with MMF, basiliximab induction and corticosteroids. The study reported that 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 (CyA)/MMF group. There was, however, an imbalance in mortality at 12 months in those patients receiving Prograf/MMF (4.2%) compared to those receiving CyA/MMF (2.4%), including cases attributed to overimmunosuppression. This study was published in the March 2007 issue of the *American Journal of Transplantation.*

A second comparative clinical study *was* the ELITE-Symphony study, supported by Hoffmann La Roche, Inc. This study was a prospective, randomized, open-label, multicenter study in four parallel groups of kidney transplant recipients. The trial randomly assigned 1,589 kidney transplant recipients to receive standard dose CyA, MMF and corticosteroids (CS); or daclizumab induction, MMF and corticosteroids in combination with low-dose CyA, Prograf or sirolimus (Siro). The primary endpoint of the study was renal function, measured by estimated glomerular filtration rates (GFR), at 12 months after transplantation. Acute rejection, graft survival and overall mortality were also assessed as secondary endpoints. This study was published in the December 2007 issue of the *New England Journal of Medicine.*

In this second study, mortality at 12 months in patients receiving Prograf/MMF (2.7%) was similar 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 (eCLcr) using the Cockcroft-Gault formula and experienced fewer efficacy failures, defined

as biopsy proven acute rejection (BPAR), graft loss, death and/or lost to follow-up in comparison to each of the other three groups: Prograf/MMF (20.4%), CyA/MMF (36.2% and 31.6%) and Siro/MMF (46.4%).

Median creatinine clearance rate, a measure of kidney function (eClcr) at 12 months was higher in the Prograf group (66.2ml/min) than in the other three groups (range, 56.9 to 60.9ml/min). The BPAR was also lowest (15.0%) in the Prograf arm when compared to the standard-dose CyA (29.0%), low-dose CyA (26.6%) or sirolimus (38.1%) groups. Graft loss excluding death was also lowest in the low-dose Prograf group (3.0%), followed by the low-dose CyA group (5.0%), the standard-dose CyA (7.2%) and the sirolimus group (7.5%).

"After more than 20 years of commitment to the fields of immunology and transplantation, Astellas remains dedicated to the advancement of the science of immunosuppression to enhance the care of transplant patients," said M. Roy First, M.D., Vice President, Therapeutic Area Head, Transplantation for Astellas. "The approval of Prograf + MMF for use in kidney transplant patients provides further evidence of Astellas' ongoing commitment to developing the field of immunology and transplantation."

About Prograf® (tacrolimus)

Prograf® (tacrolimus capsules and injection) 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. The safety and efficacy of the use of Prograf with sirolimus have not been established.

Important Safety Information

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. The physician responsible for maintenance therapy should have complete information requisite for the

Prograf is contraindicated in patients with a hypersensitivity to tacrolimus. Prograf injection is contraindicated in patients with a hypersensitivity to castor oil. **Patients receiving Prograf injection should be under continuous observation for at least the first 30 minutes following the start of infusion and at frequent intervals thereafter. If signs or symptoms of anaphylaxis occur, the infusion should be stopped.**

Insulin-dependent post-transplant diabetes mellitus was reported in 11% to 22% of Prograf-treated liver, kidney, and heart transplant patients with no prior history of diabetes mellitus. Black and Hispanic kidney transplant patients were at increased risk. Insulin dependence was reversible in 15% to 45% of patients at 1 year.

Prograf has been associated with nephrotoxicity, particularly when used in high doses. **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.**

Use of Prograf with sirolimus in heart transplant patients in a US study was associated with increased risk of wound healing complications, renal function impairment, and insulin-dependent post-transplant diabetes, and is not recommended.

Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients, in 45% and 13% of liver transplant recipients in the US and European randomized trials, respectively, and in 8% of heart transplant recipients in a European randomized trial, and may require treatment. **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, was reported in approximately 55% of liver transplant recipients in the two randomized studies. Tremor occurred more often in Prograf-treated kidney transplant (54%) and heart transplant patients (15%) compared with cyclosporine-treated patients. Seizures have occurred in adult and pediatric patients receiving Prograf. Coma and delirium also have been associated with high plasma concentrations of tacrolimus.

In post marketing experience, patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If PRES is suspected or diagnosed, immediate reduction of immunosuppression is advised. Activation of latent viral infections, including BK virus–associated nephropathy and JC virus–associated progressive multifocal leukoencephalopathy (PML), has also been reported. These viral infections may lead to serious, including fatal, outcomes.

The principal adverse reactions of Prograf include tremor, headache, hypertension, gastrointestinal disturbance, abnormal renal function, hyperglycemia, leukopenia, CMV infection, infection, and hyperlipemia.

For full prescribing information please visit www.prograf.com or call Astellas at 1-800-727-7003.

About Astellas

Astellas is a recognized leader in transplantation and has been committed to the field of immunology for more than 20 years. Dedicated to supporting the advancement of care for patients, Astellas continues to build upon its legacy and leadership in transplantation by investing in ongoing clinical research and new product development.

Astellas Pharma US, Inc., located in Deerfield, Illinois, is a U.S. affiliate of Tokyo-based Astellas Pharma Inc. Astellas is a pharmaceutical company dedicated to *"Changing tomorrow"* by improving the health of people around the world through innovative and reliable pharmaceutical products. The organization is committed to becoming a global category leader in focused areas by combining outstanding R&D and marketing capabilities. In the US, Astellas markets products in the areas of Anti-Infectives, Cardiovascular, Dermatology, Immunology and Urology. For more information about Astellas Pharma US, Inc., please visit our Web site at www.us.astellas.com or www.AstellasTransplant.com.

MEDIA NOTE – The following are available for interview regarding this FDA approval:

- Flavio Vincenti, M.D., Professor of Clinical Medicine, University of California, San Francisco, Division of Nephrology
- Goran B. Klintmalm, M.D., Ph.D., Chairman and Chief of the Baylor Regional Transplant Institute, Dallas/Fort Worth
- M. Roy First, M.D., Vice President, Therapeutic Area Head, Transplantation, Astellas Pharma US, Inc.

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