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Leading Light for Life

News Release

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Astellas Seeks Rigorous Testing and Safety-Related Labeling for Anti-Rejection Medications

Unique needs of transplant patients require special care to preserve their gift of life

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Deerfield, Ill. August 10, 2009, Astellas Pharma US, Inc. ("Astellas") announced today that the U.S. Food and Drug Administration (FDA) has substantially denied the company's Citizen Petition to ensure the safe and effective use of immunosuppressants (also called anti-rejection medications) used to prevent rejection in organ transplant patients. In their petition, Astellas requested that the FDA take additional measures to protect transplant recipients, a unique and vulnerable patient population, from substitute critical dose immunosuppressant drugs that have not demonstrated bioequivalence in rigorous clinical trials in transplant patients.

In response, Astellas plans to file a complaint for declaratory and injunctive relief in U.S. District Court in Washington, D.C. challenging the FDA's decision to apply standard bioequivalence testing for the approval of generic immunosuppressant drugs, like tacrolimus. These critical dose drugs have a narrow therapeutic margin for safety and efficacy. Under FDA's decision, bioequivalence testing is required only in healthy volunteers, not the patient population that will be treated with the new product. Bioequivalence testing measures how closely the absorption of the active ingredient in a generic drug mirrors that of an innovator drug. A generic drug must demonstrate that it falls within an acceptable range of absorption, as compared to the innovator drug. Absorption, and the clinical effect of these critical dose drugs, is affected by a number of factors, including interactions with other medications, and concurrent medical conditions. Transplant patients are at high risk for organ rejection and are often dealing with a host of medical issues, as well as taking an average of ten medications.

Additionally, the FDA denied Astellas' request for labeling changes that require physicians to be notified whenever a substituted oral formulation is about to be provided to a transplant patient so that the physician can determine whether additional drug blood concentration testing should be done to ensure the health and safety of the patient. Astellas is also challenging this part of FDA's decision.

"As a leader in the field of immunology, Astellas is firmly committed to the appropriate care and treatment of transplant patients. Transplant physicians are the most qualified to make decisions

about their patient's treatment and should be informed when the patient's medication is switched from one formulation to another," said William E. Fitzsimmons, Pharm.D., M.S., Senior Vice President, Development. "This is a specialized category of medicine and transplant patients are vulnerable to small differences in drug concentrations, which can lead to significant differences in their treatment outcome. We look forward to open discussion about this important issue."

About Organ Transplantation

There are nearly 100,000 patients on the waiting list for an organ transplant and 4,000 patients are added to the list each month. Each day, on average, seventeen patients on the list die waiting for a life-saving organ transplant.

"Due to the scarcity of organs and the potential for rejection, maintaining the delicate balance and life-preserving functions of transplanted organs is of primary importance," said Goran B. Klintmalm, M.D., Ph.D., Director, Transplantation Services, Baylor University Medical Center, Dallas, Texas, Chairman and Chief, Baylor Regional Transplant Institute, and Immediate Past-President of the American Society of Transplant Surgeons. "For more than 25 years immunosuppressant therapy has been a standard of care for transplant patients to help prevent organ rejection. It is important that the efficacy and safety profile of these drugs remain consistent to ensure transplant patients are able to receive the best possible care."

Post-transplant care is dedicated to maintaining the health of transplanted organs and a major obstacle to graft survival is rejection by the patient's immune system. Immunosuppressive drugs are the foundation of successful post-transplant care. A key to successful outcomes is patient adherence to a prescribed medication regimen. Small blood-level changes that result from changes in immunosuppressant therapy could tip the very delicate balance needed to maintain a healthy organ. Most often, the initial stages of organ rejection can be detected only by blood tests.

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.

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About Astellas Pharma US, Inc.
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 improving the health of people around the world through the provision of 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 Immunology, Urology, Anti-Infectives, Cardiovascular and Dermatology. For more information about Astellas Pharma US, Inc., please visit our website at www.us.astellas.com.

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