PROGRAF® (tacrolimus) capsules and injection
September, 2013

Indication:
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. In heart and kidney transplant recipients, it is recommended that Prograf be used in conjunction with azathioprine or mycophenolate mofetil (MMF). Therapeutic drug monitoring is recommended for all patients receiving Prograf.

Limitations of Use:
Prograf should not be used simultaneously with cyclosporine. Prograf injection should be reserved for patients unable to take Prograf capsules. Use with sirolimus is not recommended in liver and heart transplant. The safety and efficacy of Prograf with sirolimus has not been established in kidney transplant.

IMPORTANT SAFETY INFORMATION

BOXED WARNING — Malignancies and Serious Infections

- Increased risk of development of lymphoma and other malignancies, particularly of the skin, due to immunosuppression.
- Increased susceptibility to bacterial, viral, fungal, and protozoal infections, including opportunistic infections.
- Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Prograf. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Prograf is contraindicated in patients with a hypersensitivity to tacrolimus and the injection is contraindicated in patients with a hypersensitivity to HCO-60 (polyoxyl 60 hydrogenated castor oil).

Lymphomas and Other Malignancies
Patients receiving immunosuppressants, including Prograf, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. Post transplant lymphoproliferative disorder (PTLD) has been reported in immunosuppressed organ transplant recipients. The risk of PTLD appears greatest in those individuals who are Epstein Barr Virus (EBV) seronegative, a population which includes many young children.

Serious Infections
Patients receiving immunosuppressants, including Prograf, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

Polyoma Virus Infections
Patients receiving immunosuppressants, including Prograf, are at increased risk for opportunistic infections, including polyoma virus infections. Polyoma virus infections in transplant patients may have serious, and sometimes fatal, outcomes. These include polyoma virus-associated nephropathy (PVAN), mostly due to BK virus infection, and JC virus-associated progressive multifocal leukoencephalopathy (PML) which have been observed in patients receiving tacrolimus. Reductions in immunosuppression should be considered for patients who develop evidence of PVAN or PML. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft.

Cytomegalovirus (CMV) Infections
Patients receiving immunosuppressants, including Prograf, are at increased risk of developing CMV viremia and CMV disease. The risk of CMV disease is highest among transplant recipients seronegative for CMV at time of transplant who receive a graft from a CMV seropositive donor. Therapeutic approaches to limiting CMV disease exist and should be routinely provided. Patient monitoring may help detect patients at risk for CMV disease. Consideration should be given to reducing the amount of immunosuppression in patients who develop CMV viremia and/or CMV disease.

New Onset Diabetes After Transplant
Prograf was shown to cause new onset diabetes mellitus in clinical trials of kidney, liver, and heart transplantation. New onset diabetes after transplantation may be reversible in some patients. Black and Hispanic kidney transplant patients are at an increased risk. Blood glucose concentrations should be monitored closely in patients using Prograf.

013I-030-8925
Nephrotoxicity

Prograf, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity, particularly when used in high doses. Patients with impaired renal function should be monitored closely as the dosage of Prograf may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering Prograf with drugs that may be associated with renal dysfunction.

Neurotoxicity

Prograf may cause a spectrum of neurotoxicities, particularly when used in high doses. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, and coma. Patients treated with tacrolimus have been reported to develop PRES. Symptoms indicating PRES include headache, altered mental status, seizures, visual disturbances and hypertension. If PRES is suspected or diagnosed, blood pressure control should be maintained and immediate reduction of immunosuppression is advised. Coma and delirium, in the absence of PRES, have also been associated with high plasma concentrations of tacrolimus. Seizures and less severe neurotoxicities, including paresthesias, and other changes in motor function, mental status, and sensory function have been reported. Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment.

Hyperkalemia

Hyperkalemia has been reported with Prograf use. Serum potassium levels should be monitored. Careful consideration should be given prior to use of other agents also associated with hyperkalemia.

Hypertension

Hypertension is a common adverse effect of Prograf therapy and may require antihypertensive therapy.

Anaphylactic Reactions

Anaphylactic reactions have occurred with injectables containing castor oil derivatives, including IV Prograf. Prograf injection should be reserved for patients who are unable to take Prograf capsules.

Use with Sirolimus

The safety and efficacy of Prograf with sirolimus has not been established in kidney transplant patients. Use of sirolimus with Prograf in studies of de novo liver transplant patients was associated with an excess mortality, graft loss, and hepatic artery thrombosis (HAT) and is not recommended. Use of sirolimus (2 mg per day) with Prograf in heart transplant patients in a U.S. study was associated with increased risk of renal function impairment, wound healing complications, and new onset diabetes mellitus, and is not recommended.

Use with CYP3A Inhibitors and Inducers

When coadministering Prograf with strong CYP3A4-inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong inducers (e.g., rifampin, rifabutin) adjustments in the dosing regimen of Prograf and subsequent frequent monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions are recommended.

QT Prolongation

Prograf may prolong the QT/QTc interval and may cause Torsade de Pointes. Avoid Prograf in patients with congenital long QT prolongation syndrome. In patients with congestive heart failure, bradyarrhythmias, those taking certain antiarrhythmic medications or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia, consider obtaining electrocardiograms and monitoring electrolytes (magnesium, potassium, calcium) periodically during treatment.

When coadministering Prograf with other substrates and/or inhibitors of CYP3A4 that also have the potential to prolong the QT interval, a reduction in Prograf dose, frequent monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended. Use of Prograf with amiodarone has been reported to result in increased tacrolimus whole blood concentrations with or without concurrent QT prolongation.

Myocardial hypertrophy

Myocardial hypertrophy has been reported in infants, children, and adults, particularly those with high tacrolimus trough concentrations. This condition appears reversible in most cases following dose reduction or discontinuance of therapy.

Immunizations

The use of live vaccines should be avoided during treatment with tacrolimus; examples include (not limited to) the following: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

0131-030-8925
**Pure Red Cell Aplasia**
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. If PRCA is diagnosed, discontinuation of Prograf should be considered.

**Gastrointestinal Perforation**
Gastrointestinal perforation has been reported in patients treated with Prograf; all reported cases were considered to be a complication of transplant surgery or accompanied by infection, diverticulum, or malignant neoplasm. As gastrointestinal perforation may be serious or life-threatening, appropriate medical/surgical management should be instituted promptly.

**ADVERSE REACTIONS**

**Kidney Transplant:** The most common adverse reactions (≥30%) were infection, tremor, hypertension, abnormal renal function, constipation, diarrhea, headache, abdominal pain, insomnia, nausea, hypomagnesemia, urinary tract infection, hypophosphatemia, peripheral edema, asthenia, pain, hyperlipidemia, hyperkalemia, anemia.

**Liver Transplant:** The most common adverse reactions (≥40%) were tremor, headache, diarrhea, hypertension, nausea, abnormal renal function, abdominal pain, insomnia, paresthesia, anemia, pain, fever, asthenia, hyperkalemia, hypomagnesemia, and hyperglycemia.

**Heart Transplant:** The most common adverse reactions (≥15%) were abnormal renal function, hypertension, diabetes mellitus, CMV infection, tremor, hyperglycemia, leukopenia, infection, anemia, bronchitis, pericardial effusion, urinary tract infection and hyperlipemia.

**SPECIFIC POPULATIONS**

**Pregnancy:** Based on animal data may cause fetal harm. Use only if the potential benefit justifies the risk

**Nursing Mothers:** Tacrolimus is excreted in human milk, thus nursing should be discontinued taking into consideration importance of the drug to the mother.

**Hepatic/Renal Impaired Patients:** Patients should be administered the lowest recommended starting dose, with close monitoring of tacrolimus trough concentrations and renal function, and appropriate dosage adjustments.

**Please see accompanying full Prescribing Information, including Boxed Warning.** (Re-direction statement varies based on availability of the PI)