Abbreviated prescribing information of Prograf

Abbreviated prescribing information of Prograf® hard capsules

Version: 005

Composition:

Tacrolimus

Indications:

Listed in Dosage.

Dosage:

Prophylaxis of liver transplant rejection ***Adult*** *PO* 0.1-0.2 mg/kg/day bd approx 12 hr post-op. *IV* 0.01-0.05 mg/kg/day. ***Childn*** *PO* 0.3 mg/kg/day bd. *IV* 0.05 mg/kg/day. **Prophylaxis of kidney transplant rejection** ***Adult*** *PO* 0.2-0.3 mg/kg/day bd approx 24 hr post-op. *IV* 0.05-0.1 mg/kg/day. ***Childn*** *PO* 0.3 mg/kg/day bd. *IV* 0.075-0.1 mg/kg/day. **Prophylaxis of heart transplant rejection** ***Adult*** *PO* 0.075 mg/kg/day bd 5 days post-op. *IV* 0.01-0.02 mg/kg/day. ***Childn w/o Ab induction*** *IV* Initially 0.03-0.05 mg/kg/day. *PO* 0.3 mg/kg/day 8-12 hr after discontinuing IV therapy. ***W/ Ab induction*** *PO* Initially 0.1-0.3 mg/kg/day bd. **Treatment of allograft rejection:** ***in liver & kidney transplantation*** Begin w/ the initial oral dose recommended for primary immunosuppression. ***in heart transplantation*** 0.15 mg/kg/day once daily in the morning. ***Childn*** *PO* 0.2-0.3 mg/kg/day bd. Administer IV dose as continuous 24-hr infusion; ***in lung transplantation*** 0.1-0.15 mg/kg/day orally; ***in pancreas transplantation*** 0.2 mg/kg/day orally; ***in intestinal transplantation*** 0.3 mg/kg/day orally. **Rheumatoid arthritis (RA)** *PO* ***Adult*** 3 mg once daily. ***Elderly*** Initially 1.5 mg once daily for 4 wk. May be increased to 3 mg. **Lupus nephritis (LN)** *PO* ***Adult*** 3 mg once daily.

Administration:

RA & LN: Take after supper. Avoid grapefruit juice. Transplant: Take at least 1 hr before or 2-3 hr after meals. Avoid grapefruit juice.

Contraindications:

Hypersensitivity to tacrolimus or other macrolides. Hypersensitivity to any of the excipients.

Special warnings and precautions for use:

< Transplantation >

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or

prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under- or over-exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the

corresponding daily dosing regimen; alterations in formulation or regimen should only take place

under the close supervision of a transplant specialist.

During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.

Substances with potential for interaction

Inhibitors or inducers of CYP3A4 should only be co-administered with tacrolimus after consulting a transplant specialist, due to the potential for drug interactions resulting in serious adverse reactions including rejection or toxicity.

CYP3A4 inhibitors

Concomitant use with CYP3A4 inhibitors may increase tacrolimus blood levels, which could lead to serious adverse reactions, including nephrotoxicity, neurotoxicity and QT prolongation. It is recommended that concomitant use of strong CYP3A4 inhibitors (such as ritonavir, cobicistat, ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin or josamycin) with tacrolimus should be avoided. If unavoidable, tacrolimus blood levels should be monitored frequently, starting within the first few days of co-administration, under the supervision of a transplant specialist, to adjust the tacrolimus dose if appropriate in order to maintain similar tacrolimus exposure. Renal function, ECG including the QT interval, and the clinical condition of the patient should also be closely monitored.

Dose adjustment needs to be based upon the individual situation of each patient. An immediate dose reduction at the time of treatment initiation may be required.

Similarly, discontinuation of CYP3A4 inhibitors may affect the rate of metabolism of tacrolimus, thereby leading to subtherapeutic blood levels of tacrolimus, and therefore requires close monitoring and supervision of a transplant specialist.

CYP3A4 inducers

Concomitant use with CYP3A4 inducers may decrease tacrolimus blood levels, potentially increasing the risk of transplant rejection. It is recommended that concomitant use of strong CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine), with tacrolimus should be avoided. If unavoidable, tacrolimus blood levels should be monitored frequently, starting within the first few days of co-administration, under the supervision of a transplant specialist, to adjust the tacrolimus dose if appropriate, in order to maintain similar tacrolimus exposure. Graft function should also be closely monitored.

Similarly, discontinuation of CYP3A4 inducers may affect the rate of metabolism of tacrolimus, thereby leading to supratherapeutic blood levels of tacrolimus, and therefore requires close monitoring and supervision of a transplant specialist.

P-glycoprotein
Caution should be observed when co-administering tacrolimus with drugs that inhibit P-glycoprotein, as an increase in tacrolimus levels may occur. Tacrolimus whole blood levels and the clinical condition of the patient should be monitored closely. An adjustment of the tacrolimus dose may be required.

Herbal preparations

Herbal preparations containing St. John's wort (*Hypericum perforatum*) or other herbal preparations should be avoided when taking Prograf due to the risk of interactions that lead to either a decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus, or an increase in blood concentrations of tacrolimus and risk of tacrolimus toxicity.

Other interactions

The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin.

High potassium intake or potassium-sparing diuretics should be avoided.

Certain combinations of tacrolimus with drugs known to have neurotoxic effects may increase the risk of these effects.

Vaccination

Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

Nephrotoxicity

Tacrolimus can result in renal function impairment in post-transplant patients. Acute renal impairment without active intervention may progress to chronic renal impairment. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. The risk for nephrotoxicity may increase when tacrolimus is concomitantly administered with drugs associated with nephrotoxicity. Concurrent use of tacrolimus with drugs known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided, tacrolimus trough blood level and renal function should be monitored closely and dosage reduction should be considered if nephrotoxicity occurs.

Gastrointestinal disorders

Gastrointestinal perforation has been reported in patients treated with tacrolimus. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments should be considered immediately after suspected symptoms or signs occur.

Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea.

Cardiac disorders

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed on rare occasions. Most cases have been reversible, occurring primarily in children with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients, particularly young children and those receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at three months and then at 9-12 months). If abnormalities develop, dose reduction of Prograf therapy, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval and may cause *Torsades de pointes*. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, bradyarrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure.

Lymphoproliferative disorders and malignancies

Patients treated with Prograf have been reported to develop Epstein-Barr virus (EBV)-associated lymphoproliferative disorders. Patients switched to Prograf therapy should not receive anti-lymphocyte treatment concomitantly. Very young (< 2 years), EBV-VCA-negative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with Prograf. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is *per se* not indicative of lymphoproliferative disease or lymphoma.

As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown.

Posterior reversible encephalopathy syndrome (PRES)

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Eye disorders

Eye disorders, sometimes progressing to loss of vision, have been reported in patients treated with tacrolimus. Some cases have reported resolution on switching to alternative immunosuppression. Patients should be advised to report changes in visual acuity, changes in colour vision, blurred vision, or visual field defect, and in such cases, prompt evaluation is recommended with referral to an ophthalmologist as appropriate.

Infections including opportunistic infections

Patients treated with immunosuppressants, including Prograf are at increased risk for infections including opportunistic infections (bacterial, fungal, viral and protozoal) such as CMV infection, BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). Patients are also at an increased risk of infections with viral hepatitis (for example, hepatitis B and C reactivation and *de novo* infection, as well as hepatitis E, which may become chronic). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions including graft rejection that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating hepatic or renal function or neurological symptoms. Prevention and management should be in accordance with appropriate clinical guidance.

Thrombotic microangiopathy (TMA) (including haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP))

The diagnosis of TMA, including thrombotic thrombocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS), sometimes leading to renal failure or a fatal outcome, should be considered in patients presenting with haemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestation, renal impairment, and fever. If TMA is diagnosed, prompt treatment is required, and discontinuation of tacrolimus should be considered at the discretion of the treating physician.

The concomitant administration of tacrolimus with a mammalian target of rapamycin (mTOR) inhibitor (e.g., sirolimus, everolimus) may increase the risk of thrombotic microangiopathy (including haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura).

Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA.

Excipients

As Prograf contains lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The printing ink used to mark Prograf capsules (0.5mg & 1mg) contains soya lecithin. In patients who are hypersensitive to peanut or soya, the risk and severity of hypersensitivity should be weighed against the benefit of using Prograf. This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

< Rheumatoid arthritis >

For rheumatoid arthritis, treatment with this product should be limited to patients with persisting symptoms apparently attributable to the disease despite appropriate therapies with non-steroidal anti-inflammatory drugs or other antirheumatic drugs.

In patients with rheumatoid arthritis, this product should be prescribed only by physicians experienced in rheumatoid arthritis therapy. Before administration, physicians must explain the risks of treatment and the need of a long-term therapy to the patient, and ensure that the patient understands the information provided. If any abnormality is noted, the patient should be instructed to discontinue the product and contact the physician immediately for instructions.

Prograf should be administered with care in patients with rheumatoid arthritis-associated interstitial pneumonia (interstitial pneumonia may be aggravated).

The safety of this product in children has not been established in rheumatoid arthritis (no clinical experiences).

The efficacy and safety of this product in combination with methotrexate, other antirheumatic drugs, or anti-TNF α drugs have not been established in patients with rheumatoid arthritis.

In rheumatoid arthritis, the safety of the use of this product in surgery such as artificial joint replacement has not been established.

Attention should be paid to patients receiving combination therapy with two or more non-steroidal anti-inflammatory drugs, in which high incidence of elevated creatinine was reported, although the number of these cases of concomitant therapy was very low.

<Lupus nephritis>

For lupus nephritis, the efficacy and safety of this product for patients in an acute phase with high disease activity has not been established.

For patients with lupus nephritis, this product should be prescribed by physicians experienced in lupus nephritis therapy.

Patients with lupus nephritis need special attention because the renal disorder may become aggravated as the lupus nephritis progresses.

Since patients with lupus nephritis are more likely to suffer from hyperlipidemia or hypertension, etc., which are considered to be risk factors for the development of the coronary artery disease associated with systemic erythematosus, the underlying disease, patients being treated with this product should also receive appropriate therapy for these coronary diseases.

The safety of this product in children has not been established in lupus nephritis (no clinical experiences).

According to the clinical trial results up to approval, creatinine clearance decreased after 28 weeks of treatment. In the post-marketing survey (1355 cases), the incidence of creatinine increased at the end of 5-year observation period was 2.9%.

Undesirable effects:

< Transplantation >

The adverse drug reaction profile associated with immunosuppressive agents is often difficult to establish owing to the underlying disease and the concurrent use of multiple medications.

Many of the adverse drug reactions stated below are reversible and/or respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse drug reactions compared with intravenous use. Adverse drug reactions are listed below in descending order by frequency of occurrence: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Infections and infestations

As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.

Cases of CMV infection, BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Prograf.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Blood and lymphatic system disorders

common: anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal;

uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia, thrombotic microangiopathy;

rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia;

not known: pure red cell aplasia, agranulocytosis, haemolytic anaemia, febrile neutropenia.

Immune system disorders

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus.

Endocrine disorders

rare: hirsutism.

Metabolism and nutrition disorders

very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia;

common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities;

uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia.

Psychiatric disorders

very common: insomnia;

common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders;

uncommon: psychotic disorder.

Nervous system disorders

very common: tremor, headache;

common: seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders;

uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia;

rare: hypertonia;

very rare: myasthenia;

not known: posterior reversible encephalopathy syndrome (PRES).

Eye disorders

common: vision blurred, photophobia, eye disorders;

uncommon: cataract;

rare: blindness;

not known: optic neuropathy.

Ear and labyrinth disorders

common: tinnitus;

uncommon: hypoacusis;

rare: deafness neurosensory;

very rare: hearing impaired.

Cardiac disorders

common: ischaemic coronary artery disorders, tachycardia;

uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations;

rare: pericardial effusion;

very rare: *Torsades de pointes.*

Vascular disorders

very common: hypertension;

common: haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders;

uncommon: infarction, venous thrombosis deep limb, shock.

Respiratory, thoracic and mediastinal disorders

common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations;

uncommon: respiratory failures, respiratory tract disorders, asthma;

rare: acute respiratory distress syndrome.

Gastrointestinal disorders

very common: diarrhoea, nausea;

common: gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms;

uncommon: ileus paralytic, acute and chronic pancreatitis, gastrooesophageal reflux disease, impaired gastric emptying;

rare: subileus, pancreatic pseudocyst.

Hepatobiliary disorders

common: cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis;

rare: hepatic artery thrombosis, venoocclusive liver disease;

very rare: hepatic failure, bile duct stenosis.

Skin and subcutaneous tissue disorders

common: pruritus, rash, alopecias, acne, sweating increased;

uncommon: dermatitis, photosensitivity;

rare: toxic epidermal necrolysis (Lyell's syndrome);

very rare: Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders

common: arthralgia, muscle spasms, pain in extremity, back pain;

uncommon: joint disorders;

rare: mobility decreased.

Renal and urinary disorders

very common: renal impairment;

common: renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms;

uncommon: anuria, haemolytic uraemic syndrome;

very rare: nephropathy, cystitis haemorrhagic.

Reproductive system and breast disorders

uncommon: dysmenorrhoea and uterine bleeding.

General disorders and administration site conditions

common: asthenic conditions, febrile disorders, oedema, pain and discomfort, body temperature perception disturbed;

uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal;

rare: thirst, fall, chest tightness, ulcer;

very rare: fat tissue increased.

Investigations

very common: liver function tests abnormal;

common: blood alkaline phosphatase increased, weight increased;

uncommon: amylase increased, ECG investigations abnormal, heart rate and pulse investigations abnormal, weight decreased, blood lactate dehydrogenase increased;

very rare: echocardiogram abnormal, electrocardiogram QT prolonged.

Injury, poisoning and procedural complications

common: primary graft dysfunction.

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. A number of associated cases of transplant rejection have been reported (frequency cannot be estimated from available data).

Description of selected adverse reactions

Pain in extremity has been described in a number of published case reports as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS). This typically presents as a bilateral and symmetrical, severe, ascending pain in the lower extremities and may be associated with supra-therapeutic levels of tacrolimus. The syndrome may respond to tacrolimus dose reduction. In some cases, it was necessary to switch to alternative immunosuppression.

< Rheumatoid arthritis >

In the clinical studies conducted in Japan by the time of approval, the main adverse reactions or abnormal laboratory test values due to this product in 509 patients with rheumatoid arthritis (capsules 509) were abnormal renal function (20.8%, 105/506) including increased BUN (13.6%, 69/506), increased creatinine (9.3%, 47/506); gastrointestinal system disorders (14.8%, 75/508) including abdominal pain (3.7%, 19/508), diarrhoea (2.6%, 13/508), and nausea (2.2%, 11/508); and impaired glucose tolerance (8.9%, 45/505) including increased HbA1C (6.6%, 33/498), and increased blood glucose (4.4%, 22/495).

In the post-marketing clinical study and surveillance, adverse reactions (including abnormalities in clinical laboratory findings) due to this product (capsules) were observed in 1,336 (38.1%) of 3,509 patients with rheumatoid arthritis. The major adverse reactions were white blood cell count increased 2.7% (96/3,509), NAG increased 2.2% (78/3,509), BUN increased 1.7% (58/3,509), nausea 1.5% (51/3,509), HbA1c increased 1.4% (50/3,509), diabetes mellitus 1.4% (50/3,509), diarrhoea 1.3% (47/3,509), renal impairment 1.3% (46/3,509), lymphocyte count decreased 1.3% (44/3,509), β_2 microglobulin urine increased 1.3% (44/3,509).

(Notification of the reexamination results in Japan: September 2013)

In patients with rheumatoid arthritis, interstitial pneumonia may occur (incidence unknown). If respiratory symptoms such as pyrexia, cough, or dyspnea are observed, the product should be discontinued. Affected patients should be promptly examined by chest X–ray and CT scan, as well as blood testing, etc., and appropriate measures, including administration of adrenocortical hormone, etc. should be instituted, taking differential diagnosis of infection into consideration.

<Lupus nephritis>

The major adverse reactions or abnormalities in clinical laboratory findings due to this product in 65 patients with lupus nephritis (capsules 65) were increased urinary β2-microglobulin (27.3%, 12/44), increased urinary NAG (22.2%, 14/63), nasopharyngitis (15.4%, 10/65), hyperuricemia (14.1%, 9/64), leukocytosis (14.1%, 9/64), increased creatinine (12.5%, 8/64), diarrhea (12.3%, 8/65), increased blood pressure (10.8%, 7/65), and hyperglycemia (10.9%, 7/64).

Full prescribing information is available upon request.