1. NAME OF THE MEDICINAL PRODUCT

Prograf® XL 0.5 mg prolonged-release hard capsules
Prograf® XL 1 mg prolonged-release hard capsules
Prograf® XL 3 mg prolonged-release hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release hard capsule contains 0.5 mg, 1 mg, and 3 mg tacrolimus (as monohydrate).

3. PHARMACEUTICAL FORM

Prolonged-release hard capsule.

Gelatin capsules imprinted in red with "0.5 mg" on the light yellow capsule cap and " 647" on the orange capsule body, containing white powder.
Gelatin capsules imprinted in red with "1 mg" on the white capsule cap and " 677" on the orange capsule body, containing white powder.
Gelatin capsules imprinted in red with "3 mg" on the orange capsule cap and " 637" on the orange capsule body, containing white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prograf® XL is to be used concomitantly with adrenal corticosteroids and mycophenolate mofetil (MMF) in:
Prophylaxis of transplant rejection in adult kidney of liver allograft recipients;
Treatment of kidney or liver allograft rejection in adult patients previously received other immunosupressive agents.

4.2 Posology and method of administration

Prograf® XL is a once-a-day oral formulation of tacrolimus. Prograf® XL therapy requires careful monitoring by adequately qualified and equipped personnel. This medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients.

Inadvertent, unintentional or unsupervised switching of immediate- or prolonged-release formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of advese reactions, including under- or over-immunosuppression, due to clinically relevant differences in systemic 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 (see sections 4.4 and 4.8). Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

Posology
The recommended initial doses presented below are intended to act solely as a guideline. Prograf® XL is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The dose may vary depending upon the immunosuppressive regimen chosen. Prograf® XL dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring (see below under "Therapeutic drug monitoring"). If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.

In *de novo* kidney and liver transplant patients AUC_{0-24} of tacrolimus for Prograf® XL on Day 1 was 30% and 50% lower respectively, when compared with that for Prograf® at equivalent doses. By Day 4, systemic exposure as measured by trough levels is similar for both kidney and liver transplant patients with both formulations. Careful and frequent monitoring of tacrolimus trough levels is recommended in the first two weeks post-transplant with Prograf® XL to ensure adequate drug exposure in the immediate post-transplant period. As tacrolimus is a substance with low clearance, adjustments to the Prograf® XL dose regimen may take several days before steady state is achieved.

To suppress graft rejection, immunosuppression must be maintained; consequently, no limit to the duration of oral therapy can be given.

Prophylaxis of kidney transplant rejection
Prograf® XL therapy should commence at a dose of 0.20 - 0.30 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery.
Prograf® XL doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to Prograf® XL monotherapy. Post-transplant changes in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Prophylaxis of liver transplant rejection
Prograf® XL therapy should commence at a dose of 0.10 - 0.20 mg/kg/day administered once daily in the morning. Administration should commence approximately 12-18 hours after the completion of surgery.
Prograf® XL doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to Prograf® XL monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Conversion of Prograf®-treated patients to Prograf® XL
Allograft transplant patients maintained on twice daily Prograf® capsules dosing requiring conversion to once daily Prograf® XL should be converted on a 1:1 (mg:mg) total daily dose basis. Prograf® XL should be administered in the morning.

In stable patients converted from Prograf® capsules (twice daily) to Prograf® XL (once daily) on a 1:1 (mg:mg) total daily dose basis, the systemic exposure to tacrolimus (AUC_{0-24}) for Prograf® XL was approximately 10% lower than that for Prograf®. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC_{0-24}) for Prograf® XL is similar to that of Prograf®. When converting from Prograf® capsules to Prograf® XL, trough levels should be measured prior to conversion and within two weeks after conversion. Following conversion, tacrolimus trough levels should be monitored and if necessary dose adjustments made to maintain similar systemic exposure. Dose adjustments should be made to ensure that similar systemic exposure is maintained.

Conversion from ciclosporin to tacrolimus
Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy (see sections 4.4 and 4.5). The combined administration of ciclosporin and tacrolimus is not recommended. Prograf® XL therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, tacrolimus-based therapy has been initiated 12 - 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected.

Treatment of allograft rejection
Increased doses of tacrolimus, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity such as severe adverse reactions are noted (see section 4.8), the dose of Prograf® XL may need to be reduced.

Treatment of allograft rejection after kidney or liver transplantation
For conversion from other immunosuppressants to once daily Prograf® XL, treatment should begin with the initial oral dose recommended in kidney and liver transplantation respectively for prophylaxis of transplant rejection.

Treatment of allograft rejection after heart transplantation
In adult patients converted to Prograf® XL, an initial oral dose of 0.15 mg/kg/day should be administered once daily in the morning.

Treatment of allograft rejection after transplantation of other allografts
Although there is no clinical experience with Prograf® XL in lung-, pancreas- or intestine-transplanted patients, Prograf® has been used in lung-transplanted patients at an initial oral dose of 0.10 - 0.15 mg/kg/day, in pancreas-transplanted patients at an initial oral dose of 0.2 mg/kg/day and in intestinal transplantation at an initial oral dose of 0.3 mg/kg/day.

Dose adjustments in special populations
Hepatic impairment: Dose reduction may be necessary in patients with severe liver impairment in order to maintain the tacrolimus blood trough levels within the recommended target range.

Renal impairment: As the pharmacokinetics of tacrolimus are unaffected by renal function (see section 5.2), no dose adjustment is required. However, owing to the nephrotoxic potential of tacrolimus careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

Race: In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

Gender: There is no evidence that male and female patients require different doses to achieve similar trough levels.

Elderly patients: There is no evidence currently available to indicate that dosing should be adjusted in elderly patients.

Therapeutic drug monitoring
Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient aided by whole blood tacrolimus trough level monitoring.

As an aid to optimise dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood. Comparisons of concentrations from the published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC_{0-24}) is similar between the two formulations Prograf® XL and Prograf®.

Blood trough levels of tacrolimus should be monitored during the post-transplantation period. Tacrolimus blood trough levels should be determined approximately 24 hours post-dosing of Prograf® XL, just prior to the next dose. Frequent trough level monitoring in the initial two weeks post transplantation is recommended, followed by periodic monitoring during maintenance therapy. Blood trough levels of tacrolimus should also be closely monitored following conversion from Prograf® to Prograf® XL, dose adjustments, changes in the immunosuppressive regimen, or co-administration of substances which may alter tacrolimus whole blood concentrations (see section 4.5). The frequency of blood level monitoring should be based on clinical needs. As tacrolimus is a substance with low clearance, following adjustments to the Prograf® XL dose regimen it may take several days before the targeted steady state is achieved.

Data from clinical studies suggest that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the

patient when interpreting whole blood levels. In clinical practice, whole blood trough levels have generally been in the range 5 - 20 ng/ml in liver transplant recipients and 10 - 20 ng/ml in kidney and heart transplant patients in the early post-transplant period. During subsequent maintenance therapy, blood concentrations have generally been in the range of 5 - 15 ng/ml in liver, kidney and heart transplant recipients.

Method of administration
Prograf® XL is a once-a-day oral formulation of tacrolimus. It is recommended that the oral daily dose of Prograf® XL be administered once daily in the morning. Prograf® XL prolonged-release hard capsules should be taken immediately following removal from the blister. Patients should be advised not to swallow the desiccant. The capsules should be swallowed ***whole*** with fluid (preferably water). Prograf® XL should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption (see section 5.2). A forgotten morning dose should be taken as soon as possible on the same day. A double dose should not be taken on the next morning.

In patients unable to take oral medicinal products during the immediate post-transplant period, tacrolimus therapy can be initiated intravenously (see Summary of Product Characteristics for Prograf® 5 mg/ml concentrate for solution for infusion) at a dose approximately 1/5 of the recommended oral dose for the corresponding indication.

4.3 Contraindications

Prograf® XL is contraindicated in patients with a known hypersensitivity to tacrolimus, or to any of its excipients, or to other macrolides.

4.4 Special warnings and precautions for use

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 (see sections 4.2 and 4.8).

Prograf® XL is not recommended for use in children below 18 years due to limited data on safety and/or efficacy.

For treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients clinical data are not yet available for the prolonged-release formulation Prograf® XL.

For prophylaxis of transplant rejection in adult heart allograft recipients clinical data are not yet available for Prograf® XL.

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 (see section 4.5).

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 (see section 4.5).

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 (see section 4.5).

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.

Herbal preparations
Herbal preparations containing St. John's wort (*Hypericum perforatum*) should be avoided when taking Prograf® XL due to the risk of interactions that lead to a decrease in both blood concentrations and the therapeutic effect of tacrolimus (see section 4.5).

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 (see section 4.2 and 4.5).

Hyperkalemia has been reported with tacrolimus use. Serum potassium levels should be monitored. High potassium intake or potassium-sparing diuretics should be avoided (see section 4.5).

Certain combinations of tacrolimus with drugs known to have neurotoxic effects may increase the risk of these effects (see section 4.5).

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.

Gastrointestinal disorders
Gastrointestinal perforation has been reported in patients treated with tacrolimus, although all cases were considered a complication of transplant surgery or accompanied by infection, diverticulum, or malignant neoplasm. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments including surgery should be considered immediately after a suspect symptom occurs.

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 in Prograf® treated patients on rare occasions and may also occur with Prograf® XL. Most cases have been reversible, occurring 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 receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at 3 months and then at 9 -12 months). If abnormalities develop, dose reduction of Prograf® XL, 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 known risk factors for QT prolongation (including but not limited to, congenital or acquired QT prolongation, concomitant medications known to prolong the QT interval or known to increase tacrolimus exposure).

Malignancies including lymphoproliferative disorders
Patients treated with tacrolimus have been reported to develop malignant neoplasms including EBV-associated lymphoproliferative disorders, skin cancers and Kaposi's sarcoma (see section 4.8).

A combination of immunosuppressives such as antilymphocytic antibodies (e.g. basiliximab, daclizumab) given concomitantly increases the risk of EBV-associated lymphoproliferative disorders. EBV-Viral Capsid Antigen (VCA)-negative patients 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® XL. 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.

Kaposi's sarcoma, including cases with aggressive forms of disease and fatal outcomes, has been reported in patients receiving tacrolimus. In some cases, regression of Kaposi's sarcoma has been observed after reducing the intensity of immunosuppression.

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.

Opportunistic infections
Patients treated with immunosuppressants, including Prograf® XL are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), such as CMV infection, BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

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.

Nephrotoxicity
Tacrolimus can result in both acute and chronic renal function impairment in transplant patients due to its vasoconstrictive effect on renal vasculature, toxic tubulopathy and tubularinterstitial effects. Acute renal impairment can result in high serum creatinine, hyperkalemia, decreased secretion of urea and

hyperuricaemia, and is usually reversible. Chronic renal impairment is characterized by progressive renal dysfunction, increased blood urea and proteinuria. Patients with impaired renal function should be monitored closely to adjust as the dosage of tacrolimus and may need transient reduction or discontinuation. Acute renal impairment without active intervention may progress to chronic renal impairment.

Concurrent use of tacrolimus with other known nephrotoxic drugs could result in potentiation of nephrotoxicity. When concurrent use of tacrolimus with other known nephrotoxic drugs is required, monitor renal function and tacrolimus blood concentrations frequently, and dose adjustments of both tacrolimus and/or concomitant medications should be considered upon initiation, throughout concurrent treatment and at discontinuation of such concomitant drugs (see section 4.5).

Thrombotic microangiopathy (TMA) (including haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopaenic 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.

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.

Special populations
There is limited experience in non-Caucasian patients and patients at elevated immunological risk (e.g. retransplantation, evidence of panel reactive antibodies, PRA).

Dose reduction may be necessary in patients with severe liver impairment (see section 4.2).

Excipients
As Prograf® XL capsules contain 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® XL capsules 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® XL. This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Metabolic interactions
Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. Similarly, discontinuation of such products or herbal remedies may affect the rate of metabolism of tacrolimus and thereby the blood levels of tacrolimus.

Pharmacokinetics studies have indicated that the increase in tacrolimus blood levels when co-administered with inhibitors of CYP3A4 is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.

It is recommended strongly to closely monitor tacrolimus blood levels under supervision of a transplant specialist, as well as, monitor for graft function, QT prolongation (with ECG), renal function and other side effects, including neurotoxicity whenever substances which have the potential to alter CYP3A metabolism are used concomitantly, and to adjust or interrupt the tacrolimus dose if appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).
Similarly, patients should be closely monitored when using tacrolimus concomitantly with multiple substances that affect CYP3A4 as the effects on tacrolimus exposure may be enhanced or counteracted.

Medicinal products which have effects on tacrolimus are listed in the table below. The examples of drug-drug interactions are not intended to be inclusive or comprehensive and therefore the label of each drug that is co-administered with tacrolimus should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

Medicinal products which have effects on tacrolimus

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Grapefruit or grapefruit juice	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see section 4.4]*.	Avoid grapefruit or grapefruit juice.
Ciclosporin	May increase tacrolimus whole blood trough concentrations. In addition, synergistic/additive nephrotoxic effects can occur.	The simultaneous use of ciclosporin and tacrolimus should be avoided *[see section 4.4]*.
Products known to have nephrotoxic or neurotoxic effects: aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole + trimethoprim, NSAIDs, ganciclovir, acyclovir, amphotericin B, ibuprofen, cidofovir, foscarnet	May enhance nephrotoxic or neurotoxic effects of tacrolimus.	When co-administration is required, monitor renal function and other side effects and adjust tacrolimus dose if needed.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Strong CYP3A4 inhibitors: antifungal agents (e.g., ketoconazole, itraconazole, posaconazole, voriconazole), the macrolide antibiotics (e.g., telithromycin, troleandomycin, clarithromycin, josamycin), HIV protease inhibitors (e.g., ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g., telaprevir, boceprevir, and the combination of ombitasvir and paritaprevir with ritonavir, when used with and without dasabuvir), nefazodone, the pharmacokinetic enhancer cobicistat, and the kinase inhibitors idelalisib, ceritinib. Strong interactions have also been observed with the macrolide antibiotic erythromycin	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., nephrotoxicity, neurotoxicity, QT prolongation) which requires close monitoring *[see section 4.4]*. Rapid and sharp increases in tacrolimus levels may occur, as early as within 1-3 days after co-administration, despite immediate reduction of tacrolimus dose. Overall tacrolimus exposure may increase > 5 fold. When ritonavir combinations are co-administered, tacrolimus exposure may increase > 50 fold. Nearly all patients may require a reduction in tacrolimus dose and temporary interruption of tacrolimus may also be necessary. The effect on tacrolimus blood concentrations may remain for several days after co-administration is completed.	It is recommended that concomitant use should be avoided. If co-administration of a strong CYP3A4 inhibitor is unavoidable, consider omitting the dose of tacrolimus the day the strong CYP3A4 inhibitor is initiated. Reinitiate tacrolimus the next day at a reduced dose based on tacrolimus blood concentrations. Changes in both tacrolimus dose and/or dosing frequency should be individualized and adjusted as needed based on tacrolimus trough concentrations, which should be assessed at initiation, monitored frequently throughout (starting within the first few days) and re-evaluated on and after completion of the CYP3A4 inhibitor. Upon completion, appropriate dose and dosing frequency of tacrolimus should be guided by tacrolimus blood concentrations. Monitor renal function, ECG for QT prolongation, and other side effects closely.
Moderate or weak CYP3A4 inhibitors: antifungal agents (e.g., fluconazole, isavuconazole, clotrimazole, miconazole), the macrolide antibiotics (e.g., azithromycin), calcium channel blockers (e.g., nifedipine, nicardipine, diltiazem, verapamil), amiodarone, danazol, ethinylestradiol, lansoprazole, omeprazole, the HCV antivirals elbasvir/grazoprevir and glecaprevir/pibrentasvir, the CMV antiviral letermovir, and the tyrosine kinase inhibitors nilotinib, crizotinib and imatinib and (Chinese) herbal remedies containing extracts of *Schisandra sphenanthera*	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see section 4.4]*. A rapid increase in tacrolimus level may occur.	Monitor tacrolimus whole blood trough concentrations frequently, starting within the first few days of co-administration. Reduce tacrolimus dose if needed *[see section 4.2]*. Monitor renal function, ECG for QT prolongation, and other side effects closely.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see section 4.4]*.	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed *[see section 4.2]*. Monitor renal function, ECG for QT prolongation, and other side effects closely.
Strong CYP3A4 inducers: rifampicin, phenytoin, carbamazepine, apalutamide, enzalutamide, mitotane, or St. John's wort (*Hypericum perforatum*)	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see section 4.4]*. Maximal effect on tacrolimus blood concentrations may be achieved 1-2 weeks after co-administration. The effect may remain 1-2 weeks after completion of the treatment.	It is recommended that concomitant use should be avoided. If unavoidable, patients may require an increase in tacrolimus dose. Changes in tacrolimus dose should be individualized and adjusted as needed based on tacrolimus trough concentrations, which should be assessed at initiation, monitored frequently throughout (starting within the first few days) and re-evaluated on and after completion of the CYP3A4 inducer. After use of the CYP3A4 inducer has ended, tacrolimus dose may need to be adjusted gradually. Monitor graft function closely.
Moderate CYP3A4 inducers: metamizole, phenobarbital, isoniazid, rifabutin, efavirenz, etravirine, nevirapine	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see section 4.4]*.	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed *[see section 4.2]*. Monitor graft function closely.
Caspofungin	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection. Mechanism of interaction has not been confirmed.	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed *[see section 4.2]*. Monitor graft function closely.
Cannabidiol	There have been reports of increased tacrolimus blood levels during concomitant use of tacrolimus with cannabidiol.	Tacrolimus and cannabidiol should be co-administered with caution, closely monitoring for side effects. Monitor tacrolimus whole blood trough concentrations and adjust the tacrolimus dose if needed *[see sections 4.2 and 4.4]*.
Products known to have high affinity for plasma proteins, e.g., NSAIDs, oral anticoagulants, oral antidiabetics	Tacrolimus is extensively bound to plasma proteins. Possible interactions with other active substances known to have high affinity for plasma proteins should be considered.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed *[see section 4.2]*.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Prokinetic agents: metoclopramide, cimetidine and magnesium-aluminium-hydroxide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation).	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed *[see section 4.2]*. Monitor closely for renal function, for QT prolongation with ECG, and for other side effects.
Maintenance doses of corticosteroids	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see section 4.4]*.	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed *[see section 4.2]*. Monitor graft function closely.
High dose prednisolone or methylprednisolone	May have impact on tacrolimus blood levels (increase or decrease) when administered for the treatment of acute rejection.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed.
Direct-acting antiviral (DAA) therapy	May have impact on the pharmacokinetics of tacrolimus by changes in liver function during DAA therapy, related to clearance of hepatitis virus. A decrease in tacrolimus blood levels may occur. However, the CYP3A4 inhibiting potential of some DAAs may counteract that effect or lead to increased tacrolimus blood levels.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed to ensure continued efficacy and safety.

As tacrolimus treatment may be associated with hyperkalemia, or may increase pre-existing hyperkalemia, high potassium intake, or potassium-sparing diuretics (e.g. amiloride, triamterene, or spironolactone) should be avoided (see section 4.4). Care should be taken when tacrolimus is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Close monitoring of serum potassium is recommended.

Effect of tacrolimus on the metabolism of other medicinal products

Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolised by CYP3A4 may affect the metabolism of such medicinal products.

The half-life of ciclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporin and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.4).

Tacrolimus has been shown to increase the blood level of phenytoin.

As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures.

Limited knowledge of interactions between tacrolimus and statins is available. Clinical data suggest that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus.

Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine.

Mycophenolic acid. Caution should be exercised when switching combination therapy from ciclosporin, which interferes with enterohepatic recirculation of mycophenolic acid, to tacrolimus, which is devoid of this effect, as this might result in changes of mycophenolic acid exposure. Drugs which interfere with mycophenolic acid's enterohepatic cycle have potential to reduce the plasma level and efficacy of

mycophenolic acid. Therapeutic drug monitoring of mycophenolic acid may be appropriate when switching from ciclosporin to tacrolimus or vice versa.

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 (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
Human data show that tacrolimus crosses the placenta. Tacrolimus treatment can be considered in pregnant women, when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus.
The use of tacrolimus during pregnancy has been associated with preterm delivery, neonatal hyperkalemia and renal dysfunction.
A cumulative review of evidence related to the safety of the use of tacrolimus suggests that infants exposed to tacrolimus *in utero* may be at risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress.
Tacrolimus may increase hyperglycaemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly.
Tacrolimus may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure.
Females and males of reproductive potential should consider the use of appropriate contraception prior to starting treatment with tacrolimus.

Complementary evidence from a non-interventional post-authorization safety study
A post-authorization safety study analyzed 2,905 pregnancies from the Transplant Pregnancy Registry International (TPRI), assessing outcomes of pregnancies in women treated with regimens containing tacrolimus (383 reported prospectively, including 247 kidney and 136 liver transplant patients), and those on other immunosuppressants. The study results did not indicate an increased risk of major malformations. There was a trend towards a higher prevalence of spontaneous abortion among women treated with tacrolimus compared with alternative immunosuppressants. Among kidney transplant patients, there was also a trend towards a higher prevalence of pre-eclampsia in women treated with tacrolimus. Among kidney and liver transplant patients exposed to tacrolimus, 45%-55% of their live births were premature, with 75%-85% having a normal birth weight for gestational age. Similar results were observed for other immunosuppressants.

In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (see section 5.3).

Lactation
Human data demonstrate that tacrolimus is excreted in breast milk. The effects of tacrolimus on the breastfed infant, or on milk production have not been assessed. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving Prograf® XL.

Fertility
A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if tacrolimus is administered in association with alcohol.

No studies on the effects of tacrolimus (Prograf® XL) on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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

The most commonly reported adverse drug reactions (occurring in > 10% of patients) are tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalemia, infections, hypertension and insomnia.

Many of the adverse reactions stated below are reversible and/or respond to dose reduction. The frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders
Common: ischaemic coronary artery disorders, tachycardia
Uncommon: heart failures, ventricular arrhythmias and cardiac arrest, supraventricular arrhythmias, cardiomyopathies, ECG investigations abnormal, ventricular hypertrophy, palpitations, heart rate and pulse investigations abnormal
Rare: pericardial effusion
Very rare: echocardiogram abnormal, electrocardiogram QT prolonged, *Torsades de pointes*

Blood and lymphatic system disorders
Common: anaemia, thrombocytopenia, leukopenia, red blood cell analyses abnormal, leukocytosis
Uncommon: coagulopathies, pancytopenia, neutropenia, coagulation and bleeding analyses, abnormal, thrombotic microangiopathy
Rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia
Not known: pure red cell aplasia, agranulocytosis, haemolytic anaemia, febrile neutropenia

Nervous system disorders
Very common: headache, tremor
Common: nervous system disorders, seizures, disturbances in consciousness, peripheral neuropathies, dizziness, paraesthesias and dysaesthesias, writing impaired
Uncommon: encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, speech and language abnormalities, paralysis and paresis, amnesia
Rare: hypertonia
Very rare: myasthenia
Not known: posterior reversible encephalopathy syndrome (PRES)

Eye disorders
Common: eye disorders, vision blurred, photophobia
Uncommon: cataract
Rare: blindness
Not known: optic neuropathy

Ear and labyrinth disorders
Common: tinnitus
Uncommon: hypoacusis
Rare: deafness neurosensory
Very rare: hearing impaired

Respiratory, thoracic and mediastinal disorders
Common: parenchymal lung disorders, dyspnea, pleural effusion, cough, pharyngitis, nasal congestion and inflammations
Uncommon: respiratory failures, respiratory tract disorders, asthma

Rare: acute respiratory distress syndrome

Gastrointestinal disorders
Very common: diarrhoea, nausea
Common: gastrointestinal signs and symptoms, vomiting, gastrointestinal and abdominal pains, gastrointestinal inflammatory conditions, gastrointestinal haemorrhages, gastrointestinal ulceration and perforation, ascites, stomatitis and ulceration, constipation, dyspeptic signs and symptoms, flatulence, bloating and distension, loose stools
Uncommon: acute and chronic pancreatitis, amylase increased, ileus paralytic, gastrooesophageal reflux disease, impaired gastric emptying
Rare: pancreatic pseudocyst, subileus

Renal and urinary disorders
Very common: renal impairment
Common: renal failure, renal failure acute, nephropathy toxic, renal tubular necrosis, urinary abnormalities, oliguria, bladder and urethral symptoms
Uncommon: haemolytic uraemic syndrome, anuria
Very rare: nephropathy, cystitis haemorrhagic

Skin and subcutaneous tissue disorders
Common: rash, pruritus, alopecia, 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, back pain, muscle spasms, pain in extremity*
Uncommon: joint disorders
Rare: mobility decreased

Endocrine disorders
Rare: hirsutism

Metabolism and nutrition disorders
Very common: diabetes mellitus, hyperglycaemic conditions, hyperkalemia
Common: metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypophosphataemia
Uncommon: dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia

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® XL.

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).

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, skin malignancies and Kaposi's sarcoma have been reported in association with tacrolimus treatment.

Vascular disorders
Very common: hypertension
Common: thromboembolic and ischaemic events, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders
Uncommon: venous thrombosis deep limb, shock, infarction

General disorders and administration site conditions
Common: febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed, blood alkaline phosphatase increased, weight increased
Uncommon: weight decreased, influenza like illness, blood lactate dehydrogenase increased, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance
Rare: fall, ulcer, chest tightness, thirst
Very rare: fat tissue increased

Immune system disorders
Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section 4.4).

Hepatobiliary disorders
Very common: liver function tests abnormal
Common: bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice
Rare: venoocclusive liver disease, hepatic artery thrombosis
Very rare: hepatic failure

Reproductive system and breast disorders
Uncommon: dysmenorrhoea and uterine bleeding

Psychiatric disorders
Very common: insomnia
Common: confusion and disorientation, depression, anxiety symptoms, hallucination, mental disorders, depressed mood, mood disorders and disturbances, nightmare
Uncommon: psychotic disorder

*: In isolated cases, pain in extremity has been reported as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS), which typically presents as a bilateral and symmetrical, severe, ascending pain in the lower extremities.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

- email to pv@id.astellas.com or
- Pusat Farmakovigilans/MESO Nasional
  Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika,
  Psikotropika, Prekursor dan Zat Adiktif
  Badan Pengawas Obat dan Makanan
  Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
  Email: pv-center@pom.go.id
  Website: https://e-meso.pom.go.id/ADR

4.9 Overdose

Experience with overdose is limited. Several cases of accidental overdose have been reported with tacrolimus; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy and increases in blood urea nitrogen, serum creatinine and alanine aminotransferase levels.
No specific antidote to tacrolimus therapy is available. If overdose occurs, general supportive measures and symptomatic treatment should be conducted.

Based on its high molecular weight, poor aqueous solubility, and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus will not be dialysable. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Mechanism of action and pharmacodynamic effects
Tacrolimus, a macrolide, calcineurin phosphatase inhibitor.
Tacrolimus is a highly potent immunosuppressive agent and has proven activity in both *in vitro* and *in vivo* experiments.
In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection. Tacrolimus suppresses calcium-dependent signaling for transcription and synthesis of cytokines, such as interleukin-2 and gamma interferon, which are involved in early T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the expression of the interleukin-2 receptor.

Results from clinical trials performed with once-daily tacrolimus Prograf® XL
Liver transplantation
The efficacy and safety of Prograf® XL and Prograf®, both in combination with corticosteroids, was compared in 471 *de novo* liver transplant recipients. The event rate of biopsy confirmed acute rejection within the first 24 weeks after transplantation was 32.6% in the Prograf® XL group (N = 237) and 29.3% in the Prograf® group (N = 234). The treatment difference (Prograf® XL – Prograf®) was 3.3% (95% confidence interval [-5.7%, 12.3%]).The 12-month patient survival rates were 89.2% for Prograf® XL and 90.8% for Prograf®; in the Prograf® XL arm 25 patients died (14 female, 11 male) and in the Prograf® arm 24 patients died (5 female, 19 male). 12-month graft survival was 85.3% for Prograf® XL and 85.6% for Prograf®.

Kidney transplantation
The efficacy and safety of Prograf® XL and Prograf®, both in combination with mycophenolate mofetil (MMF) and corticosteroids, was compared in 667 *de novo* kidney transplant recipients. The event rate for biopsy-confirmed acute rejection within the first 24 weeks after transplantation was 18.6% in the Prograf® XL group (N = 331) and 14.9% in the Prograf® group (N = 336). The treatment difference (Prograf® XL-Prograf®) was 3.8% (95% confidence interval [-2.1%, 9.6%]). The 12-month patient survival rates were 96.9% for Prograf® XL and 97.5% for Prograf®; in the Prograf® XL arm 10 patients died (3 female, 7 male) and in the Prograf® arm 8 patients died (3 female, 5 male). 12-month graft survival was 91.5% for Prograf® XL and 92.8% for Prograf.

The efficacy and safety of Prograf®, ciclosporin and Prograf® XL, all in combination with basiliximab antibody induction, MMF and corticosteroids, was compared in 638 *de novo* kidney transplant recipients. The incidence of efficacy failure at 12 months (defined as death, graft loss, biopsy-confirmed acute rejection, or lost to follow-up) was 14.0% in the Prograf® XL group (N = 214), 15.1% in the Prograf® group (N = 212) and 17.0% in the ciclosporin group (N = 212). The treatment difference was -3.0% (Prograf® XL-ciclosporin) (95.2% confidence interval [-9.9%, 4.0%]) for Prograf® XL vs. ciclosporin and -1.9% (Prograf®-ciclosporin) (95.2% confidence interval [-8.9%, 5.2%]) for Prograf® vs. ciclosporin. The

12-month patient survival rates were 98.6% for Prograf® XL, 95.7% for Prograf® and 97.6% for ciclosporin; in the Prograf® XL arm 3 patients died (all male), in the Prograf® arm 10 patients died (3 female, 7 male) and in the ciclosporin arm 6 patients died (3 female, 3 male). 12-month graft survival was 96.7% for Prograf® XL, 92.9% for Prograf® and 95.7% for ciclosporin.

Clinical efficacy and safety of Prograf® capsules bid in primary organ transplantation

In prospective studies oral Prograf® was investigated as primary immunosuppressant in approximately 175 patients following lung, 475 patients following pancreas and 630 patients following intestinal transplantation. Overall, the safety profile of oral Prograf® in these published studies appeared to be similar to what was reported in the large studies, where Prograf® was used as primary treatment in liver, kidney and heart transplantation. Efficacy results of the largest studies in each indication are summarised below.

Lung transplantation

The interim analysis of a recent multicentre study using oral Prograf® discussed 110 patients who underwent 1:1 randomisation to either tacrolimus or ciclosporin. Tacrolimus was started as continuous intravenous infusion at a dose of 0.01 to 0.03 mg/kg/day and oral tacrolimus was administered at a dose of 0.05 to 0.3 mg/kg/day. A lower incidence of acute rejection episodes for tacrolimus- versus ciclosporin-treated patients (11.5% versus 22.6%) and a lower incidence of chronic rejection, the bronchiolitis obliterans syndrome (2.86% versus 8.57%), was reported within the first year after transplantation. The 1-year patient survival rate was 80.8% in the tacrolimus and 83% in the ciclosporin group.

Another randomised study included 66 patients on tacrolimus versus 67 patients on ciclosporin. Tacrolimus was started as continuous intravenous infusion at a dose of 0.025 mg/kg/day and oral tacrolimus was administered at a dose of 0.15 mg/kg/day with subsequent dose adjustments to target trough levels of 10 to 20 ng/ml. The 1-year patient survival was 83% in the tacrolimus and 71% in the ciclosporin group, the 2-year survival rates were 76% and 66%, respectively. Acute rejection episodes per 100 patient-days were numerically fewer in the tacrolimus (0.85 episodes) than in the ciclosporin group (1.09 episodes). Obliterative bronchiolitis developed in 21.7% of patients in the tacrolimus group compared with 38.0% of patients in the ciclosporin group ($p = 0.025$). Significantly more ciclosporin-treated patients ($n = 13$) required a switch to tacrolimus than tacrolimus-treated patients to ciclosporin ($n = 2$) ($p = 0.02$) (Keenan et al., Ann Thoracic Surg 1995;60:580).

In an additional two-centre study, 26 patients were randomised to the tacrolimus versus 24 patients to the ciclosporin group. Tacrolimus was started as continuous intravenous infusion at a dose of 0.05 mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/ml. The 1-year survival rates were 73.1% in the tacrolimus versus 79.2% in the ciclosporin group. Freedom from acute rejection was higher in the tacrolimus group at 6 months (57.7% versus 45.8%) and at 1 year after lung transplantation (50% versus 33.3%).

The three studies demonstrated similar survival rates. The incidences of acute rejection were numerically lower with tacrolimus in all three studies and one of the studies reported a significantly lower incidence of bronchiolitis obliterans syndrome with tacrolimus.

Pancreas transplantation

A multicentre study using oral Prograf® included 205 patients undergoing simultaneous pancreas-kidney transplantation who were randomised to tacrolimus ($n = 103$) or to ciclosporin ($n = 102$). The initial oral per protocol dose of tacrolimus was 0.2 mg/kg/day with subsequent dose adjustments to target trough levels of 8 to 15 ng/ml by Day 5 and 5 to 10 ng/ml after Month 6. Pancreas survival at 1 year was significantly superior with tacrolimus: 91.3% versus 74.5% with ciclosporin ($p < 0.0005$), whereas renal graft survival was similar in both groups. In total 34 patients switched treatment from ciclosporin to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy.

Intestinal transplantation

Published clinical experience from a single centre on the use of oral Prograf® for primary treatment following intestinal transplantation showed that the actuarial survival rate of 155 patients (65 intestine alone, 75 liver and intestine, and 25 multivisceral) receiving tacrolimus and prednisone was 75% at 1 year, 54% at 5 years, and 42% at 10 years. In the early years the initial oral dose of tacrolimus was 0.3 mg/kg/day. Results continuously improved with increasing experience over the course of 11 years. A variety of innovations, such as techniques for early detection of Epstein-Barr (EBV) and CMV infections, bone

marrow augmentation, the adjunct use of the interleukin-2 antagonist daclizumab, lower initial tacrolimus doses with target trough levels of 10 to 15 ng/ml, and most recently allograft irradiation were considered to have contributed to improved results in this indication over time.

5.2 Pharmacokinetic properties

Absorption
In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Available tacrolimus is generally rapidly absorbed. Prograf® XL is a prolonged-release formulation of tacrolimus resulting in an extended oral absorption profile with an average time to maximum blood concentration (C_{max}) of approximately 2 hours (t_{max}).
Absorption is variable and the mean oral bioavailability of tacrolimus (investigated with the Prograf® formulation) is in the range of 20% - 25% (individual range in adult patients 6% - 43%). The oral bioavailability of Prograf® XL was reduced when it was administered after a meal. Both the rate and extent of absorption of Prograf® XL were reduced when administered with food.
Bile flow does not influence the absorption of tacrolimus and therefore treatment with Prograf® XL may commence orally.
A strong correlation exists between AUC and whole blood trough levels at steady-state for Prograf® XL. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

Distribution
In man, the disposition of tacrolimus after intravenous infusion may be described as biphasic.
In the systemic circulation, tacrolimus binds strongly to erythrocytes resulting in an approximate 20:1 distribution ratio of whole blood/plasma concentrations. In plasma, tacrolimus is highly bound (> 98.8%) to plasma proteins, mainly to serum albumin and α-1-acid glycoprotein.
Tacrolimus is extensively distributed in the body. The steady-state volume of distribution based on plasma concentrations is approximately 1300 l (healthy subjects). Corresponding data based on whole blood averaged 47.6 l.

Metabolism
Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4 (CYP3A4) and the cytochrome P450-3A5 (CYP3A5). Tacrolimus is also considerably metabolised in the intestinal wall. There are several metabolites identified. Only one of these has been shown *in vitro* to have immunosuppressive activity similar to that of tacrolimus. The other metabolites have only weak or no immunosuppressive activity. In systemic circulation only one of the inactive metabolites is present at low concentrations. Therefore, metabolites do not contribute to the pharmacological activity of tacrolimus.

Excretion
Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of tacrolimus, or corticosteroid-induced increased metabolism, are considered to be responsible for the higher clearance rates observed following transplantation.
The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood is approximately 43 hours.
Following intravenous and oral administration of ^{14}C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2% of the radioactivity was eliminated in the urine. Less than 1% of unchanged tacrolimus was detected in the urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

5.3 Preclinical safety data

The kidneys and the pancreas were the primary organs affected in toxicity studies performed in rats and baboons. In rats, tacrolimus caused toxic effects to the nervous system and the eyes. Reversible cardiotoxic effects were observed in rabbits following intravenous administration of tacrolimus.
Embryofoetal toxicity was observed in animal studies.

Tacrolimus subcutaneously administered to male rats at a doses of 2 or 3 mg/kg/day (1.6 to 6.4 times the clinical dose range based on body surface area) resulted in a dose-related decrease in sperm count. Tacrolimus given orally at 1.0 mg/kg (0.8 to 2.2 times the clinical dose range based on body surface area) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and adverse effects on female reproduction which were indicated by a higher rate of post-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (2.6 to 6.9 times the clinical dose range based on body surface area), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Hypromellose
Ethylcellulose
Lactose monohydrate
Magnesium stearate.

Capsule shell:
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Red iron oxide (E 172)
Sodium laurilsulfate
Gelatin.

Printing ink (Opacode S-1-15083):
Shellac
Lecithin (soya)
Simeticone
Red iron oxide (E 172)
Hydroxypropylcellulose.

6.2 Incompatibility

Tacrolimus is not compatible with PVC. Tubing, syringes and other equipment used to prepare or administer the tacrolimus products (infusion or suspension of capsule contents) should not contain PVC.

6.3 Shelf life

3 years
After opening the aluminium wrapper: 1 year

6.4 Special precaution for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Prograf XL 0.5 mg
Box of 1 aluminium pouch @ 5 blister @ 10 capsules.
Reg. No.: DKI1308000303A1

Prograf XL 1 mg
Box of 1 aluminium pouch @ 5 blister @ 10 capsules.

Reg. No.: DKI1308000303B1

Prograf XL 3 mg
Box of 1 aluminium pouch @ 5 blister @ 10 capsules.
Reg. No.: DKI1708000303D1

Special precaution for disposal and other handling
Based on immunosuppressive effects of tacrolimus, inhalation or direct contact with skin or mucous membranes by the formulations for injection or powder contained in tacrolimus products should be avoided during preparation. If such contact occurs, wash the skin and flush the affected eye or eyes.

HARUS DENGAN RESEP DOKTER

Manufactured by: Astellas Ireland, Co., Ltd., Killorglin, County Kerry, V93 FC86, Ireland

Marketing Authorization Holder: PT. Combiphar, JI. Raya Simpang 383, Padalarang, Bandung Barat, Jawa Barat, Indonesia

Imported and Marketed by: PT. Astellas Pharma Indonesia, Jakarta, Indonesia

Leaflet: Informasi untuk Pasien
Prograf® XL 0.5mg Kapsul lepas lambat
Prograf® XL 1mg Kapsul lepas lambat
Prograf® XL 3mg Kapsul lepas lambat
Tacrolimus

Bacalah leaflet ini dengan seksama sebelum anda mengonsumsi obat ini karena laeflet ini mengandung informasi penting untuk anda.

- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya lagi.
- Jika anda memiliki pertanyaan lebih lanjut, silahkan tanya kepada dokter atau apoteker anda.
- Obat ini diresepkan hanya untuk anda. Jangan memberikannya kepada orang lain, hal tersebut mungkin akan membahayakan bagi mereka, walaupun tanda gejala dan penyakit mereka sama seperti anda.
- Jika anda mengalami efek samping, bicarakan dengan dokter atau apoteker anda. Hal ini termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini. Lihat nomor 4.

Apa saja yang ada dalam leaflet ini

1. Apa itu Prograf® XL dan kegunaannya

Prograf® XL mengandung zat aktif *tacrolimus*. Obat ini termasuk imunosupresan (obat yang menekan sistem kekebalan/sistem imun tubuh). Setelah transplantasi organ (hati, ginjal), sistem kekebalan tubuh anda akan mencoba untuk menolak organ baru. Prograf® XL digunakan untuk mengontrol respon kekebalan tubuh anda, memunginkan tubuh anda untuk menerima organ transplantasi.

Anda juga mungkin diberikan Prograf® XL pada saat terjadi penolakan berkelanjutan terhadap organ transplantasi hati dan ginjal anda bila pengobatan sebelumnya tidak mampu mengontrol respon kekebalan tubuh anda.

Prograf® XL digunakan untuk orang dewasa.

2. Apa yang perlu diketahui sebelum mengonsumsi Prograf® XL

Jangan konsumsi Prograf® XL

Jika anda alergi (hipersensitif) terhadap *tacrolimus* atau bahan lain dari Prograf® XL (lihat nomor 6). Jika anda alergi terhadap sirolimus atau antibiotik golongan makrolida (seperti eritromisin, klaritromisin, josamycin).

Peringatan dan perhatian

Prograf® dan Prograf® XL keduanya mengandung zat aktif, *tacrolimus*. Namun, Prograf® XL dikonsumsi sehari sekali, sedangkan Prograf® dikonsumsi dua kali sehari. Hal ini dikarenakan Prograf® XL merupakan sediaan *tacrolimus* kapsul lepas lambat (dilepas secara perlahan dalam waktu yang lama). Prograf® XL tidak dapat saling menggantikan dengan Prograf® tanpa pengawasan dari dokter.

Beritahu dokter atau apoteker sebelum menggunakan Prograf® XL:

- Jika anda mengonsumsi obat-obatan yang disebutkan pada bagian “Prograf® XL dan obat-obatan lain”
- Jika anda pernah atau sedang mengalami gangguan hati
- Jika anda mengalami diare lebih dari 1 hari
- Jika anda mengalami nyeri perut hebat disertai atau tidak disertai dengan gejala lain seperti perasaanmengingil , demam, mual atau muntah
- Jika anda memiliki perubahan aktivitas listrik jantung yang disebut “perpanjangan QT”
- Jika Anda memiliki atau memiliki riwayat kerusakan pada pembuluh darah terkecil, yang diketahui dengan *thrombotic microangiopathy/thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome.* Bicarakan pada dokter Anda jika anda mengalami demam, memar pada bagian bawah kulit (seperti bintik merah), kelelahan tanpa sebab, kebingungan, kulit atau menguning, penurunan volume urin, kehilangan pandangan dan kejang (lihat nomor 4). Ketika tacrolimus digunakan bersamaan dengan sirolimus atau everolimus, risiko mengalami gejala-gejala tersebut dapat meningkat.

Hindari mengonsumsi pengobatan herbal, seperti St. John’s wort (*Hypericum perforatum*) atau produk herbal lainnya karena dapat berpengaruh pada keefektifan dan dosis Prograf® XL yang anda terima. Jika Anda ragu, konsultasikan kepada dokter sebelum mengonsumsi produk atau pengobatan herbal apapun.

Dokter anda mungkin perlu menyesuaikan dosis Prograf® XL anda.

Anda harus tetap berkomunikasi secara rutin dengan dokter anda. Dari waktu ke waktu, dokter anda mungkin perlu untuk melakukan tes darah, urin, fungsi hati, mata untuk mengatur dosis Prograf® XL yang tepat untuk anda.

Anda harus membatasi kontak dengan sinar matahari dan UV (ultraviolet) selama anda mengonsumsi Prograf® XL. Hal ini dikarenakan imunosupresan dapat meningkatkan resiko kanker kulit. Gunakan pakaian pelindung yang tepat dan gunakan tabir surya dengan SPF yang tinggi.

Yang Perlu Diperhatikan saat Penanganan:
Kontak langsung dengan setiap bagian tubuh Anda seperti kulit atau mata, atau menghirup cairan injeksi, atau bubuk yang terkandung dalam produk tacrolimus harus dihindari selama penanganan. Jika kontak seperti itu terjadi, cucilah kulit dan mata.

Anak-anak dan remaja
Penggunaan Prograf® XL tidak dianjurkan untuk anak-anak dan remaja dibawah 18 tahun.

Prograf® XL dan obat-obatan lain

Beritahu dokter atau apoteker anda jika anda mengonsumsi atau baru saja mengonsumsi obat-obatan lain, termasuk obat yang diperoleh tanpa resep dokter dan obat herbal.

Prograf® XL tidak dianjurkan dikonsumsi dengan siklosporin (obat yang juga digunakan untuk mencegah penolakan transplantasi organ).

Jika Anda harus bertemu dokter lain selain spesialis transplantasi Anda, beritahukan kepada dokter Anda bahwa Anda sedang mengonsumsi tacrolimus. Dokter Anda mungkin perlu untuk berkonsultasi kepada spesialis transplantasi Anda apabila Anda harus menggunakan obat-obatan lain yang dapat meningkatkan atau menurunkan kadar tacrolimus dalam darah Anda.

Kadar Prograf® XL dalam darah dapat dipengaruhi oleh obat-obatan lain yang anda gunakan dan kadar dalam darah dari obat lain yang anda gunakan dapat dipengaruhi oleh penggunaan Prograf® XL, hal ini mungkin memerlukan perubahan peningkatan atau penurunan dosis Prograf® XL.

Beberapa pasien mengalami peningkatan kadar tacrolimus dalam darah ketika menggunakan obat-obatan lain. Hal ini dapat menyebabkan efek samping serius, seperti gangguan ginjal, gangguan sistem saraf, dan gangguan ritme jantung (lihat nomor 4).
Sebuah efek yang menyebabkan peningkatan kadar Prograf® XL dalam darah dapat terjadi sangat cepat setelah penggunaan obat-obatan lain, sehingga pemantauan lanjutan secara terus menerus terhadap kadar Prograf® XL dalam darah mungkin perlu dilakukan dalam beberapa hari pertama penggunaan obat-obatan lain dan lebih sering ketika penggunaan obat-obatan lain dilanjutkan. Beberapa obat yang dapat menyebabkan penurunan kadar tacrolimus dalam darah dapat meningkatkan resiko penolakan organ transplantasi. Secara khusus, anda harus memberitahu dokter anda jika anda sedang atau baru saja mengonsumsi obat-obatan seperti:

- Obat antijamur dan antibiotik, antibiotik makrolida yang biasanya digunakan untuk mengobati infeksi misalnya ketokenazol, flukonazol, itrakonazol, posaconazol, vorikonazol, klotrimazol, isavuconazol, miconazol, caspofungin, telithromycin, eritromisin, klaritomisin, josamin, azitromisin, rifampisin, rifabutin, dan isoniazid
- Letermovir, digunakan untuk mencegah penyakit yang disebabkan oleh *human cytomegalovirus*
- Penghambat enzim protease pada virus human immunodeficiency (misalnya ritonavir, nelfinavir, saquinavir), obat booster cobicistat, dan kombinasi tablet, atau inhibitor HIV *non-nucleoside reverse transcriptase* (efavirenz, etravirine, nevirapine) yang digunakan untuk mengobati infeksi HIV
- Penghambat enzim protease pada virus hepatitis C (contoh telaprevir, boceprevir, kombinasi ombitasvir/paritaprevir/ritonavir dengan atau tanpa dasabuvir, elbasvir/grazoprevir, dan glecaprevir/pibrentasvir), yang digunakan untuk pengobatan hepatitis C.
- Nilotinib dan imatinib, idelalisib, ceritinib, crizotinib, apalutamide, enzalutamide, atau mitotane (digunakan untuk mengobati kanker-kanker tertentu)
- Mycophenolic acid, digunakan untuk menekan sistem imun untuk mencegah penolakan transplantasi
- Obat-obatan untuk ulkus/luka lambung dan refluks/kembalinya isi lambung ke tenggorokan (misalnya omeprazol, lansoprazol atau simetidin)
- Antiemetik, digunakan untuk mengobati mual dan muntah (misalnya metoklopramid)
- Cisaprid atau antasida magnesium-aluminium hidroksida, digunakan untuk mengobati maag
- Pil kontrasepsi atau perawatan hormon lain dengan etinilestradiol, perawatan hormon dengan danazol
- Obat yang digunakan untuk mengobati tekanan darah tinggi atau masalah jantung (misalnya nifedipin, nicardipin, diltiazem dan verapamil)
- Obat anti aritmia (amiodaron) digunakan untuk mengontrol aritmia (ketidakseimbangan detak jantung)
- Obat yang dikenal sebagai “statin” digunakan untuk mengobati kolesterol tinggi dan trigliserida
- Karbamasepin, fenitoin atau fenobarbital, digunakan untuk mengobati epilepsi
- Kortikosteroid prednisolon dan metilprednisolon, yang termasuk kelas kortikosteroid yang digunakan untuk mengobati radang atau menekan sistem kekebalan tubuh (misalnya dalam penolakan transplantasi).
- Nefazodone, digunakan untuk mengobati depresi.
- Obat herbal yang mengandung *St John’s Wort* (*Hypericum perforatum*) atau ekstrak *Schisandra sphenanthera*

- Cannabidiol (yang digunakan antara lain sebagai obat kejang).

Beritahu dokter anda jika anda menerima pengobatan untuk Hepatitis C. Obat-obatan untuk Hepatitis C dapat mengubah fungsi hati anda dan dapat mempengaruhi kadar tacrolimus dalam darah. Kadar tacrolimus dalam darah dapat berkurang atau meningkat tergantung pada obat-obatan yang diresepkan untuk Hepatitis C. Dokter anda mungkin perlu untuk meninjau kadar tacrolimus dalam darah dan membuat penyesuaian dosis Prograf® XL setelah anda memulai pengobatan Hepatitis C.

Beritahu kepada dokter anda jika anda mengonsumsi atau perlu mengonsumsi ibuprofen (digunakan untuk mengobati demam, peradangan dan nyeri), antibiotik (kotrimoksazol, vankomisin, atau antibiotik golongan aminoglikosida seperti gentamisin), amfoterisin B (digunakan untuk mengobati infeksi jamur) atau antiviral (digunakan untuk mengobati infeksi virus misalnya asiklovir, gansiklovir, cidofovir, atau foscarnet). Ini mungkin memperburuk ginjal atau masalah sistem saraf ketika dikonsumsi bersama-sama dengan Prograf® XL.

Dokter anda juga perlu tahu jika anda mengonsumsi suplemen kalium atau diuretik (obat yang membuang kelebihan cairan dalam tubuh) tertentu yang digunakan untuk gagal jantung, hipertensi dan penyakit ginjal, (misalnya amiloride, triamterene atau spironolakton), *non-steroid anti-inflammatory drugs* (NSAIDs, misalnya ibuprofen) digunakan untuk demam, peradangan dan nyeri, antikoagulan (pengencer darah), atau obat-obatan oral untuk diabetes, sementara anda mengonsumsi Prograf® XL.

Jika anda memerlukan vaksinasi, mohon beritahukan dokter anda.

Prograf® XL dengan makanan dan minuman

Hindari jeruk dan jeruk bali (termasuk dalam bentuk jus) saat pengobatan dengan Prograf® XL, karena dapat mempengaruhi kadar dalam darah.

Kehamilan dan menyusui

Jika anda, mungkin berencana untuk hamil, tanyakan pada dokter anda untuk saran sebelum menggunakan Prograf® XL. Sebuah studi menilai hasil kehamilan pada wanita yang diobati dengan takrolimus dan mereka yang diobati dengan imunosupresan lainnya. Meskipun tidak ada bukti yang cukup dalam studi ini untuk menarik kesimpulan, tingkat keguguran yang lebih tinggi dilaporkan di antara pasien transplantasi hati dan ginjal yang diobati dengan takrolimus, serta tingkat yang lebih tinggi di antara pasien transplantasi ginjal dengan preeklampsia (hipertensi persisten yang terkait dengan kehilangan protein dalam urin yang berkembang selama kehamilan atau periode pasca persalinan). Tidak ditemukan perbedaan tingkat risiko cacat lahir mayor (kelainan yang mempengaruhi struktur organ vital dan membutuhkan tindakan segera untuk bertahan hidup) antara penggunaan takrolimus dengan immunosupresan lain.

Takrolimusdapat masuk ke dalam ASI. Oleh karena itu, anda tidak boleh menyusui selama menggunakan Prograf® XL.

Mengemudi dan menggunakan mesin

Jangan mengemudi atau menjalankan alat atau mesin jika anda merasa pusing atau mengantuk, atau memiliki masalah penglihatan setelah mengonsumsi Prograf® XL. Efek ini lebih sering terjadi apabila anda juga mengonsumsi alkohol.

Prograf® XL mengandung laktosa dan lesitin (lemak alami kedelai)
Prograf® XL mengandung laktosa (gula susu). Bila anda telah diberitahu oleh dokter anda bahwa anda memiliki intoleransi laktosa, hubungi dokter anda sebelum mengonsumsi obat ini.
Tinta cetak yang digunakan pada kapsul Prograf® XL mengandung lesitin kedelai. Jika anda alergi terhadap kacang atau kedelai, bicaralah dengan dokter anda untuk menentukan apakah anda harus menggunakan obat ini.

3. Bagaimana cara mengonsumsi Prograf® XL

Selalu gunakan Prograf® XL sesuai petunjuk dokter anda. Anda harus menanyakan kepada dokter atau apoteker anda apabila anda tidak yakin. Obat ini hanya boleh diresepkan untuk anda oleh dokter yang berpengalaman dalam pengobatan pasien transplantasi.

Pastikan bahwa anda menerima obat *tacrolimus* yang sama setiap kali anda menebus resep anda, kecuali spesialis transplantasi anda telah setuju untuk mengubah obat *tacrolimus* yang berbeda. Obat ini harus dikonsumsi sekali sehari. Jika tampilan obat ini tidak sama seperti biasanya, atau jika instruksi dosis diubah, bicaralah dengan dokter atau apoteker sesegera mungkin untuk memastikan bahwa anda memiliki obat yang tepat.

Dosis awal untuk mencegah penolakan organ transplantasi akan dijelaskan oleh dokter anda dihitung berdasarkan berat badan anda. Dosis harian awal setelah transplantasi umumnya akan berada pada kisaran:

0.10 – 0.30 mg / kg berat badan / hari

tergantung pada organ yang ditransplantasi. Saat mengobati penolakan, dosis yang sama dapat digunakan.

Dosis anda tergantung pada kondisi umum anda dan obat imunospuresan apa yang anda konsumsi.

Setelah memulai pengobatan Prograf® XL, tes darah rutin akan dilakukan oleh dokter untuk menentukan dosis yang benar. Setelah tes darah rutin dokter anda akan menentukan dosis yang benar dan menyesuaikan dosis dari waktu ke waktu. Dokter biasanya akan mengurangi dosis Prograf® XL anda setelah kondisi anda telah stabil. Dokter anda akan memberitahu berapa banyak kapsul yang harus dikonsumsi.

Anda perlu untuk mengonsumsi Prograf® XL setiap hari selama anda perlu imunosupresi untuk mencegah penolakan organ transplantasi anda. Anda harus tetap berkomunikasi secara rutin dengan dokter anda.

Prograf® XL dikonsumsi secara oral sekali sehari di pagi hari. Konsumsi Prograf® XL pada waktu perut kosong atau 2 sampai 3 jam setelah makan. Tunggu minimal 1 jam sampai makan berikutnya. Konsumsi kapsul segera setelah membuka blister. Kapsul harus ditelan **utuh** dengan segelas air. Jangan menelan bahan pengering yang ada dalam pembungkus *foil*.

Jika anda mengonsumsi Prograf® XL lebih banyak dari yang seharusnya
Jika anda secara tidak sengaja mengonsumsi Prograf® XL terlalu banyak, segera hubungi dokter anda atau Unit Gawat Darurat rumah sakit terdekat.

Jika anda lupa mengonsumsi Prograf® XL
Jika anda lupa mengonsumsi Prograf® XL di pagi hari, konsumsi sesegera mungkin di hari yang sama. Jangan mengonsumsi dosis ganda pada pagi hari berikutnya.

Jika anda berhenti mengonsumsi Prograf® XL
Menghentikan pengobatan Prograf® XL dapat meningkatkan resiko penolakan organ transplantasi anda. Jangan menghentikan pengobatan anda kecuali kalau dokter yang memberitahu anda untuk melakukannya.

Jika anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, silahkan menanyakan pada dokter atau apoteker anda.

4. Kemungkinan efek samping

Seperti obat-obat lainnya, Prograf® XL dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya.

Prograf® XL menurunkan mekanisme pertahanan tubuh anda (sistem kekebalan tubuh) yang tidak baik dampaknya dalam memerangi infeksi. Oleh karena itu, anda mungkin akan lebih rentan terhadap infeksi saat mengonsumsi Prograf® XL.

Efek samping berat dapat terjadi, termasuk reaksi alergi dan anafilaksis (reaksi alergi berat yang mengancam jiwa). Tumor jinak dan ganas telah dilaporkan selama pengobatan menggunakan Prograf® XL.
Beritahukan dokter Anda segera jika Anda mengalami atau mungkin mengalami efek samping serius berikut:

Efek samping serius yang umum (dapat terjadi pada 1 dari 10 orang):
- Luka pada saluran cerna: nyeri perut yang parah disertai atau tidak dengan gejala lain, seperti menggigil, demam, mual atau muntah
- Kurangnya fungsi organ transplantasi
- Penglihatan kabur

Efek samping serius yang tidak umum (dapat terjadi pada 1 dari 100 orang):
- *Thrombotic microangiopathy* (kerusakan pada pembuluh darah terkecil) termasuk h*aemolytic uraemic syndrome* (HUS), suatu kondisi dengan gejala berikut: rendah atau tidak ada output urin (gagal ginjal akut), kelelahan ekstrim, menguningnya kulit atau mata (*jaudince*) dan memar abnormal atau perdarahan dan tanda-tanda infeksi.

Efek samping serius yang jarang (dapa terjadi pada 1 dari 1.000 orang):
- Trombotik trombositopenik purpura: suatu kondisi yang melibatkan kerusakan pada pembuluuh darah terkecil ditandai dengan demam dan memar di bawah kulit yang mungkin muncul sebagai bintik-bintik merah, dengan atau tanpa disertai rasa lelah yang ekstrim yang tidak dapat dijelaskan, kebingungan, menguningnya kulit atau mata (*jaundice*), dengan gejala gagal ginjal akut (output urin rendah atau tidak ada), kehilangan penghilatan dan kejang.
- *Toxic epidermal necrolysis*: pengelupasan dan melepuh pada kulit atau selaput lendir, peradangan pada kulit yang data terjadi pada area tubuh yang luas.
- Kebutaan

Efek samping serius yang sangat jarang (dapat terjadi pada 1 dari 10.000 orang):

- Sindrom Stevens-Johnson: nyeri pada kulit yang meluas, wajah bengkak, penyakit serius dengan kulit, mulut, mata dan area kelamin yang melepuh, gatal-gatal, lidah bengkak, ruam kulit yang menyebar berwarna merah atau ungu, ganti kulit.
- *Torsades de Pointes*: perubahan frekuensi jantung yang dapat disertai atau tidak dengan gejala, seperti nyeri dada (angina), pingsan, vertigo atau mual, palpitasi (detak jantung terasa) dan kesulitan bernapas.

Efek samping serius – frekuensi tidak diketahui (frekuensi tidak dapat dihitung dari data yang tersedia):
- Infeksi oportunistik (infeksi yang disebabkan bakteri, jamur, virus dan protozoa yang tidak berbahaya pada orang sehat namun menyerang orang dengan kekebalan tubuh lemah): diare berkepanjangan, demam dan sakit tenggorokan.
- Tumor jinak dan ganas telah dilaporkan sebagai akibat pengobatan dengan imunosupresi, termasuk kanker kulit ganas dan kanker kulit langka yang mungkin termasuk lesi/luka kulit yang dikenal sebagai sarkoma Kaposi. Gejalanya termasuk perubahan kulit seperti muncul warna baru atau perubahan warna kulit yang sudah ada, lesi, atau benjolan.
- Kasus dari aplasia sel darah merah (penurunan yang sangat parah dari jumlah sel darah merah), anemia hemolitik (penurunan jumlah sel darah merah karena kerusakan abnormal disertai kelelahan) dan febril neutropenia (penurunan salah satu tipe sel darah putih yang melawan infeksi, disertai dengan demam) telah dilaporkan. Tidak diketahui secara pasti seberapa sering efek samping ini terjadi. Anda dapat tidak memiliki gejala atau bergantung pada tingkat keparahan, anda mungkin merasa: kelelahan, apatis, kulit pucat abnormal, nafas pendek, pusing, sakit kepala, nyeri dada, dan dingin pada tangan dan kaki.
- Kasus agranulositosis (penuruanan sel darah putih yang tinggi disertai dengan ulkus/luka di mulut, demam dan infeksi). Anda mungkin tidak memiliki gejala atau Anda mungkin merasa demam mendadak, menggigil dan sakit tenggorokan.
- Reaksi alergi dan anafilaksis dengan gejala berikut: ruam gatal mendadak (gatal-gatal), pembengkakan tangan, kaki, pergelangan kaki, wajah, bibir, mulut atau tenggorokan (yang dapat menyebabkan kesulitan dalam menelan atau bernapas) dan Anda mungkin merasa Anda akan pingsan.
- *Posterior Reversible Encephalopathy Syndrome* (PRES): sakit kepala, kebingungan, perubahan perasaan, kejang, dan gangguan penglihatan. Hal ini dapat menjadi gejala dari gangguan yang dinamakan sindrom posterior reversible encephalopathy, yang telah dilaporkan pada beberapa pasien yang menggunakan tacrolimus.
- Neuropati optik (ketidaknormalan sarafmata): gangguan dengan penglihatan Anda seperti penglihatan kabur, gangguan pada saat melihat warna, kesulitan untuk melihat detil atau batasan pada jarak pandang anda.

<u>Efek samping yang tercantum di bawa ini juga dapat terjadi setelah menerima Prograf® XL dan dapat menjadi serius:</u>

<u>Efek samping yang sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang):</u>
- Peningkatan kadar gula dalam darah, diabetes melitus, peningkatan kalium darah
- Sulit tidur
- Gemetar, sakit kepala
- Peningkatan tekanan darah
- Tes fungsi hati yang abnormal
- Diare, mual

- Masalah ginjal

Efek samping yang umum (dapat mempengaruhi sampai dengan 1 dari 10 orang):
- Berkurangnya hasil hitung sel darah (keping darah, sel darah merah atau putih), meningkatnya hasil hitung sel darah putih, perubahan pada hasil hitung sel darah merah (terlihat pada hasil tes darah)
- Pengurangan magnesium, fosfat, kalium, kalsium atau natrium dalam darah, kelebihan cairan, peningkatan asam urat atau lipid dalam darah, penurunan nafsu makan, peningkatan keasaman darah, perubahan lain dalam garam darah (terlihat pada hasil tes darah)
- Gejala cemas, kebingungan dan disorientasi, depresi, perubahan suasana hati, mimpi buruk, halusinasi, gangguan mental
- Kejang, gangguan kesadaran, kesemutan dan mati rasa (terkadang nyeri) pada tangan dan kaki, pusing, gangguan dalam kemampuan menulis, gangguan sistem saraf
- Peningkatan sensitifitas terhadap cahaya, gangguan mata
- Denging suara di telinga
- Berkurangnya aliran darah di pembuluh jantung, detak jantung lebih cepat
- Perdarahan, penyumbatan sebagian atau lengkap dari pembuluh darah, penurunan tekanan darah
- Sesak napas, perubahan dalam jaringan paru-paru, pengumpulan cairan di area paru-paru, radangtenggorokan, batuk, gejala seperti flu
- Radang atau maag yang menyebabkan sakit perut atau diare, pendarahan di perut, radang atau ulkus di mulut, pengumpulan cairan di area perut, muntah, nyeri perut, gangguan pencernaan, sulit buang air besar, perut kembung, mencret, masalah perut
- Gangguan saluran empedu, kulit menguning karena masalah hati, kerusakan jaringan hati dan radang hati
- Gatal, ruam, rambut rontok, jerawat, peningkatan keringat
- Nyeri pada sendi, kaki atau punggung, kejang otot
- Kurangnya fungsi ginjal, berkurangnya produksi urin, gangguan atau nyeri buang air kecil
- Lemah, demam, pengumpulan cairan dalam tubuh, rasa sakit dan tidak nyaman, peningkatan enzim alkali fosfatase dalam darah, peningkatan berat badan, perasaan perubahan suhu tubuh yang menganggu

Efek samping yang tidak biasa terjadi (dapat mempengaruhi hingga 1 dari 100 orang):
- Perubahan dalam pembekuan darah, penurunan semua jumlah sel darah (terlihat pada hasil tes darah)
- Dehidrasi
- Mengurangi protein atau gula dalam darah, peningkatan fosfat dalam darah
- Koma, perdarahan di otak, stroke, kelumpuhan, gangguan otak, kelainan dalam berbicara, masalah memori
- Pandangan kabur karena kelainan pada lensa mata
- Pendengaran terganggu
- Denyut jantung tidak teratur, denyut jantung berhenti, penurunan kinerja jantung, gangguan otot jantung, pembesaran otot jantung, peningkatan detak jantung, EKG/rekam jantung tidak normal, denyut jantung dan denyut nadi tidak normal
- Pembekuan darah dalam pembuluh vena pada anggota tubuh, shock (kondisi darurat yang mengancam jiwa)
- Kesulitan bernapas, gangguan saluran pernapasan, asma
- Obstruksi usus (kelainan pada usus), peningkatan level darah dari enzim amilase, refluks (keluarnya isi lambung ke tenggorokan), penundaan proses pengosongan lambung
- Peradangan pada kulit, sensasi rasa terbakar di bawah sinar matahari
- Gangguan sendi

- Ketidakmampuan untuk buang air kecil, nyeri haid dan perdarahan haid yang tidak normal
- Kerusakan pada beberapa organ, seperti penyakit influenza, peningkatan sensitifitas terhadap panas dan dingin, rasa tertekan pada dada, gelisah, peningkatan enzim laktat dehidrogenase dalam darah, penurunan berat badan

Efek samping yang jarang terjadi (dapat mempengaruhi hingga 1 dari 1.000 orang):
- Pendarahan kecil pada kulit karena pembekuan darah
- Peningkatan kekakuan otot
- Ketulian
- Pengumpulan cairan di sekitar jantung
- Sesak napas akut
- Pembentukan kista/benjolan di pankreas
- Masalah dengan aliran darah di hati
- Pertumbuhan rambut tidak normal
- Haus, pingsan, rasa sesak di dada, mobilitas menurun, ulkus

Efek samping yang sangat jarang terjadi (dapat mempengaruhi sampai 1 dari 10.000 orang):
- Lemah otot
- EKG tidak normal
- Kerusakan pada hati
- Nyeri saat buang air kecil disertai darah dalam urin
- Peningkatan jaringan lemak

Pelaporan efek samping
Jika Anda mengalami efek samping, segera hubungi dokter atau apoteker Anda. Hal ini termasuk kemungkinan efek samping yang tidak tercantum pada leaflet ini. Anda dapat melaporkan efek samping secara langsung melalui email pv@id.astellas.com. Dengan melaporkan efek samping yang terjadi, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

5. Bagaimana cara menyimpan Prograf® XL

Jauhkan dari pandangan dan jangkauan anak-anak.

Jangan gunakan Prograf® XL setelah tanggal kadaluarsa yang tertera pada karton setelah “Exp”. Tanggal kadaluarsa mengacu pada hari terakhir dari bulan itu. Gunakan semua kapsul lepas lambat dalam waktu 1 tahun setelah membuka pembungkus aluminium.

Simpan pada kemasan aslinya untuk melindungi dari kelembapan.

Jangan membuang obat-obatan melalui air limbah atau limbah rumah tangga. Tanyakan apoteker anda bagaimana cara membuang obat-obatan yang tidak anda gunakan lagi. Langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lain

Apa yang terkandung dalam Prograf® XL:
- Zat aktif adalah *Tacrolimus*.
  Tiap kapsul Prograf® XL 0.5mg mengandung 0.5mg tacrolimus (sebagai monohidrat)
  Tiap kapsul Prograf® XL 1mg mengandung 1mg tacrolimus (sebagai monohidrat)
  Tiap kapsul Prograf® XL 3mg mengandung 3mg tacrolimus (sebagai monohidrat)

- Bahan lainnya adalah :
  Isi kapsul: *hypermellose, ethylcellulose, lactose, magnesium stearate*.
  Cangkang kapsul: *titanium oxide* (E171), *yellow iron oxide* (E172), *red iron oxide* (E172), *sodium lauryl sulphate*, gelatin.
  Tinta cetak: *shellac*, lesitin (kedelai), simetikon, *red iron dioxide*(E172), *hydroxyprophylcellulose*.

Seperti apakah bentuk Prograf® XL dan isi dari kemasannya
Prograf® XL 0.5mg kapsul lepas lambat adalah kapsul gelatin keras dicetak dengan warna merah tulisan "0.5mg" pada tutup kapsul berwarna kuning terang dan "✶647" pada badan kapsul oranye, mengandung bubuk putih.
Prograf® XL 1mg kapsul lepas lambat adalah kapsul gelatin keras dicetak dengan warna merah tulisan "1mg" pada tutup kapsul berwarna putih dan "✶677" pada badan kapsul oranye, mengandung bubuk putih.
Prograf® XL 3mg kapsul lepas lambat adalah kapsul gelatin keras dicetak dengan warna merah tulisan "3mg" pada tutup kapsul berwarna oranye dan "✶637" pada badan kapsul oranye, mengandung bubuk putih.

Isi satu dus:
Dus berisi 1 aluminium pouch @ 5 blister @ 10 kapsul

Batas kadaluarsa: 3 tahun
Setelah pembungkus alumunium dibuka: 1 tahun

Perhatian khusus untuk penyimpanan
Jangan simpan pada suhu di atas 30ºC
Tetap simpan pada kemasan asli untuk melindungi dari kelembaban.

HARUS DENGAN RESEP DOKTER.

Nomor Ijin Edar:
Prograf XL 0,5mg: DKI1308000303A1
Prograf XL 1mg: DKI1308000303B1
Prograf XL 3mg: DKI1708000303D1

Pemegang Izin Edar dan Produsen
Pemegang Izin Edar
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