ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Modigraf 0.2 mg granules for oral suspension
Modigraf 1 mg granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Modigraf 0.2 mg granules for oral suspension
Each sachet contains 0.2 mg tacrolimus (as monohydrate).

Excipient with known effect:
Each sachet contains 94.7 mg lactose (as monohydrate).

Modigraf 1 mg granules for oral suspension
Each sachet contains 1 mg tacrolimus (as monohydrate).

Excipient with known effect:
Each sachet contains 473 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral suspension.
White granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of transplant rejection in adult and paediatric, kidney, liver or heart allograft recipients.

Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients.

4.2 Posology and method of administration

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. Modigraf is a granular formulation of tacrolimus, for twice-a-day administration. Modigraf therapy requires careful monitoring by adequately qualified and equipped personnel.

Posology
The recommended initial doses presented below are intended to act solely as a guideline. Modigraf 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. Modigraf 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.

Careful and frequent monitoring of tacrolimus trough levels is recommended in the first 2 weeks post-transplant to ensure adequate exposure to the active substance in the immediate post-transplant period. As tacrolimus is a substance with low clearance, it may take several days after adjustments to the Modigraf dose regimen before steady state is achieved (see below under “Therapeutic drug monitoring” and section 5.2).

Modigraf should not be switched with the prolonged-release capsules (Advagraf) as a clinically relevant difference in bioavailability between the two formulations cannot be excluded. In general, 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 undesirable effects, including under- or overimmunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding 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.

Prophylaxis of kidney transplant rejection
Adults
Oral Modigraf therapy should commence at 0.20 - 0.30 mg/kg/day administered as 2 divided doses (e.g. morning and evening). Administration should commence within 24 hours after the completion of surgery.
If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 0.05 - 0.10 mg/kg/day (with Prograf 5 mg/ml concentrate for solution for infusion) should be initiated as a continuous 24-hour infusion.

Paediatric population
An initial oral dose of 0.30 mg/kg/day should be administered in 2 divided doses (e.g. morning and evening). If the clinical condition of the patient prevents oral dosing, an initial intravenous dose of 0.075 – 0.100 mg/kg/day (with Prograf 5 mg/ml concentrate for solution for infusion) should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and paediatric patients
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus-based dual therapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Prophylaxis of liver transplant rejection
Adults
Oral Modigraf therapy should commence at 0.10 - 0.20 mg/kg/day administered as 2 divided doses (e.g. morning and evening). Administration should commence approximately 12 hours after the completion of surgery.
If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 0.01 - 0.05 mg/kg/day (with Prograf 5 mg/ml concentrate for solution for infusion) should be initiated as a continuous 24-hour infusion.

Paediatric population
An initial oral dose of 0.30 mg/kg/day should be administered in 2 divided doses (e.g. morning and evening). If the clinical condition of the patient prevents oral dosing, an initial intravenous dose of 0.05 mg/kg/day (with Prograf 5 mg/ml concentrate for solution for infusion) should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and paediatric patients
Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus monotherapy.
Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Prophylaxis of heart transplant rejection
Adults
Modigraf can be used with antibody induction (allowing for delayed start of tacrolimus therapy) or alternatively in clinically stable patients without antibody induction.
Following antibody induction, oral Modigraf therapy should commence at a dose of 0.075 mg/kg/day administered as 2 divided doses (e.g. morning and evening). Administration should commence within 5 days after the completion of surgery as soon as the patient's clinical condition is stabilised. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 0.01 to 0.02 mg/kg/day (with Prograf 5 mg/ml concentrate for solution for infusion) should be initiated as a continuous 24-hour infusion.
An alternative strategy was published where oral tacrolimus was administered within 12 hours post transplantation. This approach was reserved for patients without organ dysfunction (e.g. renal dysfunction). In that case, an initial oral tacrolimus dose of 2 to 4 mg per day was used in combination with mycophenolate mofetil and corticosteroids or in combination with sirolimus and corticosteroids.

Paediatric population
Tacrolimus has been used with or without antibody induction in paediatric heart transplantation.
In patients without antibody induction, if tacrolimus therapy is initiated intravenously, the recommended starting dose is 0.03 - 0.05 mg/kg/day (with Prograf 5 mg/ml concentrate for solution for infusion) as a continuous 24-hour infusion targeted to achieve tacrolimus whole blood concentrations of 15 - 25 nanogram/ml. Patients should be converted to oral therapy as soon as clinically practicable. The first dose of oral therapy should be 0.30 mg/kg/day starting 8 to 12 hours after discontinuing intravenous therapy.
Following antibody induction, if Modigraf therapy is initiated orally, the recommended starting dose is 0.10 - 0.30 mg/kg/day administered as 2 divided doses (e.g. morning and evening).

Dose adjustment during post-transplant period in adults and paediatric patients
Tacrolimus doses are usually reduced in the post-transplant period. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Conversion between Modigraf and Prograf tacrolimus formulations
In healthy subjects the systemic exposure to tacrolimus (AUC) for Modigraf was approximately 18% higher than that for Prograf capsules when administered as single doses. There are no safety data available on the use of Modigraf granules following a temporary switch from Prograf or Advagraf in critically ill patients.

Stable allograft recipients maintained on Modigraf granules, requiring conversion to Prograf capsules, should be converted on a 1:1 mg:mg total daily dose basis. If equal doses are not possible, the total daily dose of Prograf should be rounded-up to the nearest amount possible, with the higher dose given in the morning and the lower dose in the evening.

Similarly, for conversion of patients from Prograf capsules to Modigraf granules, the total daily Modigraf dose should preferably be equal to the total daily Prograf dose. If conversion on the basis of equal quantities is not possible, the total daily dose of Modigraf should be rounded down to the nearest total daily dose possible with sachets 0.2 mg and 1 mg.
The total daily dose of Modigraf granules should be administered in 2 equal doses. If equal doses are not possible, then the higher dose should be administered in the morning and the lower dose in the evening. Modigraf sachets must not be used partially.

Example: Total daily dose Prograf capsules given as 1 mg in the morning and 0.5 mg in the evening. Then give a total daily dose of Modigraf 1.4 mg divided as 0.8 mg in the morning and 0.6 mg in the evening.

Tacrolimus trough levels should be measured prior to conversion and within 1 week after conversion. 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. Tacrolimus 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 tacrolimus doses, 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 Modigraf may need to be reduced.

Treatment of allograft rejection after kidney or liver transplantation – adults and paediatric patients
For conversion from other immunosuppressants to twice daily Modigraf, treatment should begin with the initial oral dose recommended for primary immunosuppression.

Treatment of allograft rejection after heart transplantation therapy – adults and paediatric patients
In adult patients converted to Modigraf, an initial oral dose of 0.15 mg/kg/day should be administered in 2 divided doses (e.g. morning and evening).
In paediatric patients converted to tacrolimus, an initial oral dose of 0.20 - 0.30 mg/kg/day should be administered in 2 divided doses (e.g. morning and evening).

Treatment of allograft rejection after transplantation of other allografts
The dose recommendations for lung, pancreas and intestinal transplantation are based on limited prospective clinical trial data with the Prograf formulation. 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.

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_{12}) and systemic exposure (AUC_{0-12}) is similar between the 2 formulations Modigraf granules and Prograf capsules.

Blood trough levels of tacrolimus should be monitored during the post-transplantation period. Tacrolimus blood trough levels should be determined approximately 12 hours post-dosing of Modigraf granules, just prior to the next dose. Frequent trough level monitoring in the initial 2 weeks post transplantation is recommended, followed by periodic monitoring during maintenance therapy. Blood trough levels should be monitored at least twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be closely monitored when clinical signs of toxicity or acute rejection are observed, following conversion between Modigraf granules to Prograf capsules, 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, it may take several days after adjustments to the Modigraf dose regimen before the targeted steady state is achieved (see section 5.2).

Data from clinical studies suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 nanogram/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 nanogram/ml in liver transplant recipients and 10 - 20 nanogram/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 nanogram/ml in liver, kidney and heart transplant recipients.

Special populations
Hepatic impairment
Dose reduction may be necessary in patients with severe liver impairment in order to maintain the 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 older people.

Paediatric population
In general, paediatric patients require doses 1½ - 2 times higher than the adult doses to achieve similar blood levels.

Method of administration
Tacrolimus therapy is generally initiated by the oral route. If necessary, tacrolimus dosing may commence by administering Modigraf granules suspended in water, via nasogastric tubing.

It is recommended that the oral daily dose of Modigraf be administered in 2 divided doses (e.g. morning and evening).

Modigraf granules 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).

The required dose is calculated from the weight of the patient, using the minimum number of sachets possible. 2 ml of water (at room temperature) should be used per 1 mg tacrolimus to produce a suspension (up to a maximum of 50 ml, depending on body weight) in a cup. Materials containing polyvinyl chloride (PVC) should not be used (see section 6.2). Granules are added to the water and stirred. It is not advised to use any liquids or utensils to empty the sachets. The suspension can be drawn up via a syringe or swallowed directly by the patient. Thereafter the cup is rinsed once with the same quantity of water and the rinsings consumed by the patient. The suspension should be administered immediately after preparation.

4.3 Contraindications

Hypersensitivity to tacrolimus or to any of the excipients listed in section 6.1.
Hypersensitivity to other macrolides.

4.4 Special warnings and precautions for use

There are no safety data available on the use of Modigraf granules following a temporary switch from Prograf or Advagraf in critically ill patients.

Modigraf should not be switched with Advagraf as a clinically relevant difference in bioavailability between the two formulations cannot be excluded. Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse reactions, including graft rejection, or other adverse reactions 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 formulations or regimen should only take place under the close supervision of a transplant specialist (see sections 4.2 and 4.8).

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.

P-glycoprotein
Caution should be observed when co-administering tacrolimus with drugs that inhibit P-glycoprotein,

as an increase in tacrolimus levels may occur. Tacrolimus whole blood levels and the clinical condition of the patient should be monitored closely. An adjustment of the tacrolimus dose may be required (see section 4.5).

Herbal preparations
Herbal preparations containing St. John's wort (*Hypericum perforatum*) or other herbal preparations should be avoided when taking Modigraf due to the risk of interactions that lead to either a decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus, or an increase in blood concentrations of tacrolimus and risk of tacrolimus toxicity (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 sections 4.2 and 4.5).

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 risks 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.

Nephrotoxicity
Tacrolimus can result in renal function impairment in post-transplant patients. Acute renal impairment without active intervention may progress to chronic renal impairment. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. The risk for nephrotoxicity may increase when tacrolimus is concomitantly administered with drugs associated with nephrotoxicity (see section 4.5). Concurrent use of tacrolimus with drugs known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided, tacrolimus trough blood level and renal function should be monitored closely and dosage reduction should be considered if nephrotoxicity occurs.

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

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

Cardiac disorders
Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed on rare occasions. Most cases have been reversible, occurring with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients, particularly young children and those receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at 3 months and then at 9-12 months). If abnormalities develop, dose reduction of Modigraf, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval and may cause *Torsades de pointes*. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, bradyarrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or

acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure (see section 4.5).

Lymphoproliferative disorders and malignancies
Patients treated with tacrolimus have been reported to develop Epstein-Barr Virus (EBV)-associated lymphoproliferative disorders (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 Modigraf. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is *per se* not indicative of lymphoproliferative disease or lymphoma.

As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).

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.

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

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

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

Thrombotic microangiopathy (TMA) (including haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP))
The diagnosis of TMA, including thrombotic thrombocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS), sometimes leading to renal failure or a fatal outcome, should be considered in patients presenting with haemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestation, renal impairment, and fever. If TMA is diagnosed, prompt treatment is required, and discontinuation of tacrolimus should be considered at the discretion of the treating physician.
The concomitant administration of tacrolimus with a mammalian target of rapamycin (mTOR) inhibitor (e.g., sirolimus, everolimus) may increase the risk of thrombotic microangiopathy (including haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura).

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

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 Modigraf granules contain lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. This medicine contains less than 1 mmol sodium (23 mg) per sachet, 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 CYP3A4 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.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
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.	Concurrent use of tacrolimus with drugs known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided, monitor renal function and other side effects and adjust tacrolimus dose if needed.
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.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
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.
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.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Moderate CYP3A4 inducers: metamizole, phenobarbital, isoniazid rifabutin, efavirenz, etravirine, nevirapine; weak CYP3A4 inducers: flucloxacillin	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 (P-gp inhibitor)	There have been reports of increased tacrolimus blood levels during concomitant use of tacrolimus with cannabidiol. This may be due to inhibition of intestinal P-glycoprotein, leading to increased bioavailability of tacrolimus.	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]*.
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	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed to ensure continued efficacy and safety.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
	of HCV 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.	

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) (see section 4.4).

As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, 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 phenazone.

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 Fertility, pregnancy and lactation

Pregnancy
Human data show that tacrolimus crosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse reactions on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. To date, no other relevant epidemiological data are

available. 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. In case of *in utero* exposure, monitoring of the newborn for the potential adverse events of tacrolimus is recommended (in particular effects on the kidneys).There is a risk for premature delivery (< 37 week) (incidence of 66 of 123 births, i.e. 53.7%; however, data showed that the majority of the newborns had normal birth weight for their gestational age) as well as for hyperkalaemia in the newborn (incidence 8 of 111 neonates, i.e. 7.2%) which, however normalises spontaneously.
In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (see section 5.3). Tacrolimus affected fertility in male rats (see section 5.3).

Breast-feeding
Human data demonstrate that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving tacrolimus.

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 (Modigraf) on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile
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 reactions (occurring in > 10% of patients) are tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension and insomnia.

List of adverse reactions
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 adverse reactions are presented in order of decreasing seriousness.

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 Modigraf.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Blood and lymphatic system disorders

common:	anaemia, 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

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

Endocrine disorders

rare:	hirsutism

Metabolism and nutrition disorders

very common:	diabetes mellitus, hyperglycaemic conditions, hyperkalaemia
common:	metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypophosphataemia
uncommon:	dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia

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

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

Cardiac disorders

common:	ischaemic coronary artery disorders, tachycardia
uncommon:	heart failures, ventricular arrhythmias and cardiac arrest, supraventricular arrhythmias, cardiomyopathies, ventricular hypertrophy, palpitations
rare:	pericardial effusion
very rare:	*Torsades de pointes*

Vascular disorders

very common:	hypertension
common:	thromboembolic and ischaemic events, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders
uncommon:	venous thrombosis deep limb, shock, infarction

Respiratory, thoracic and mediastinal disorders

common:	parenchymal lung disorders, dyspnoea, 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, ileus paralytic, gastrooesophageal reflux disease, impaired gastric emptying
rare:	pancreatic pseudocyst, subileus

Hepatobiliary disorders

common:	bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice
rare:	venoocclusive liver disease, hepatic artery thrombosis
very rare:	hepatic failure

Skin and subcutaneous tissue disorders

common:	rash, pruritus, alopecias, acne, sweating increased
uncommon:	dermatitis, photosensitivity
rare:	toxic epidermal necrolysis (Lyell's syndrome)
very rare:	Stevens Johnson syndrome

Musculoskeletal and connective tissue disorders

common:	arthralgia, back pain, muscle spasms, pain in extremity
uncommon:	joint disorders
rare:	mobility decreased

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

Reproductive system and breast disorders

uncommon:	dysmenorrhoea and uterine bleeding

General disorders and administration site conditions

common:	febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed
uncommon:	influenza like illness, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance
rare:	fall, ulcer, chest tightness, thirst
very rare:	fat tissue increased

Investigations

very common:	liver function tests abnormal
common:	blood alkaline phosphatase increased, weight increased
uncommon:	amylase increased, ECG investigations abnormal, heart rate and pulse investigations abnormal, weight decreased, blood lactate dehydrogenase increased
very rare:	echocardiogram abnormal, electrocardiogram QT prolonged

Injury, poisoning and procedural complications

common:	primary graft dysfunction

Description of selected adverse reactions

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

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 the national reporting system listed in Appendix V.

4.9 Overdose

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 concentrations 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. In isolated patients with very high plasma levels, haemofiltration or -diafiltration have been effective in reducing toxic concentrations. In cases of oral intoxication, gastric lavage and/or the use of adsorbents (such as activated charcoal) may be helpful, if used shortly after intake.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, calcineurin inhibitors, ATC code: L04AD02

Mechanism of action and pharmacodynamic effects

At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of lymphokine genes.
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 T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines (such as interleukins-2, -3, and γ-interferon) and the expression of the interleukin-2 receptor.

Clinical efficacy and safety of tacrolimus administered twice daily in other primary organ transplantation

In prospective published studies oral tacrolimus (given as Prograf capsules) 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 tacrolimus in these published studies appeared to be similar to what was reported in the large studies, where tacrolimus 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 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 nanogram/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 ($n = 2$) ($p = 0.02$).

In an additional 2-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 nanogram/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 3 studies demonstrated similar survival rates. The incidences of acute rejection were numerically lower with tacrolimus in all 3 studies and one of the studies reported a significantly lower incidence of bronchiolitis obliterans syndrome with tacrolimus.

Pancreas transplantation

A multicentre study 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 nanogram/ml by Day 5 and 5 to 10 nanogram/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 tacrolimus 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 nanogram/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.
Modigraf granules are an immediate-release formulation of tacrolimus for twice daily dosing. Following oral administration of Modigraf granules peak concentrations (C_{max}) of tacrolimus in blood are on average achieved in approximately 2 to 2.5 hours.
Absorption of tacrolimus is variable. Results of a single dose bioequivalence study with adult healthy volunteers showed that Modigraf granules were approximately 20% more bioavailable than the Prograf capsules. Mean oral bioavailability of tacrolimus (investigated with the Prograf capsules formulation) is in the range of 20 - 25% (individual range in adult patients 6 - 43%, in paediatric kidney transplant patients 3 - 77%). The oral bioavailability of tacrolimus was reduced when it was administered after a meal.
Bile flow does not influence the absorption of tacrolimus and therefore treatment with Modigraf granules may commence orally.
In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile.

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases both the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.
In stable liver transplant patients, the oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat (34% of calories) content. Decreases in AUC (27%) and C_{max} (50%), and an increase in t_{max} (173%) in whole blood were evident.
In a study of stable renal transplant patients who were administered tacrolimus immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12%) and C_{max} (15 to 38%), and an increase in t_{max} (38 to 80%) in whole blood were evident.
A strong correlation exists between AUC and whole blood trough levels at steady-state for Modigraf. 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 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 was approximately 43 hours. In adult and paediatric liver transplant patients, it averaged 11.7 hours and 12.4 hours, respectively, compared with 15.6 hours in adult kidney transplant recipients. Increased clearance rates contribute to the shorter half-life observed in transplant recipients.

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.

Paediatric data
In paediatric liver transplant patients the mean oral bioavailability of tacrolimus (investigated with the Modigraf granules) is 26% ± 23% (individual range in paediatric liver transplant patients 4 - 80%). Data on oral bioavailability of Modigraf in other indications is not available.
After oral administration (0.30 mg/kg/day) to paediatric liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in the majority of patients.
In paediatric liver and kidney transplant patients, values for total body clearance of 2.3 ± 1.2 ml/min/kg and 2.1 ± 0.6 ml/min/kg, respectively, have been observed. Highly variable age dependent total body clearance and half-life were observed in limited paediatric clinical investigations, especially in early childhood.
The half-life in paediatric transplant patients averages approximately 12 hours.

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. When tacrolimus is administered intravenously as rapid infusion/bolus injection at a dose of 0.1 to 1.0 mg/kg, QTc prolongation has been observed in some animal species. Peak blood concentrations achieved with these doses were above 150 nanogram/mL which is more than 6-fold higher than mean peak concentrations observed with Modigraf in clinical transplantation.
Embryofoetal toxicity was observed in rats and rabbits and was limited to doses that caused significant toxicity in maternal animals. In rats, female reproductive function including birth was impaired at toxic doses and the offspring showed reduced birth weights, viability and growth.
A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose (E464)
Croscarmellose sodium (E468)

6.2 Incompatibilities

Tacrolimus is not compatible with PVC (polyvinylchloride) plastics. Materials used to prepare and administer the suspension, e.g. drinking vessels, cups, or tubing, must not contain PVC.

6.3 Shelf life

3 years.

After preparation, the suspension should be administered immediately.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Sachets consisting of layers of polyethylene terephtalate (PET), aluminium (Al) and polyethylene (PE).

Pack size: carton box containing 50 sachets.

6.6 Special precautions 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, powder or granule contained in tacrolimus products should be avoided during preparation. If such contact occurs, wash the skin and flush the affected eye or eyes.

7. MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Modigraf 0.2 mg granules for oral suspension
EU/1/09/523/001

Modigraf 1 mg granules for oral suspension
EU/1/09/523/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 May 2009
Date of latest renewal: 17 Feb 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Astellas Ireland Co. Ltd
Killorglin
Co. Kerry, V93FC86
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENT OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Modigraf 0.2 mg granules for oral suspension
tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 0.2 mg tacrolimus (as monohydrate).

3. LIST OF EXCIPIENTS

Also contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

50 sachets containing granules for oral suspension.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Suspend the granules in water.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

After preparation, the suspension should be administered immediately.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/523/001

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

modigraf 0.2 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET FOIL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Modigraf 0.2 mg granules for oral suspension
tacrolimus
oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Astellas Pharma Europe B.V.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Modigraf 1 mg granules for oral suspension
tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 1 mg tacrolimus (as monohydrate).

3. LIST OF EXCIPIENTS

Also contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

50 sachets containing granules for oral suspension.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Suspend the granules in water.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

After preparation, the suspension should be administered immediately.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/523/002

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

modigraf 1 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET FOIL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Modigraf 1 mg granules for oral suspension
tacrolimus
oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Astellas Pharma Europe B.V.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Modigraf 0.2 mg, granules for oral suspension
Modigraf 1 mg, granules for oral suspension
Tacrolimus

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Modigraf is and what it is used for
2. What you need to know before you take Modigraf
3. How to take Modigraf
4. Possible side effects
5. How to store Modigraf
6. Contents of the pack and other information

1. What Modigraf is and what it is used for

Modigraf contains the active substance tacrolimus. It is an immunosuppressant. Following your organ transplant (e.g., liver, kidney, heart), your body's immune system will try to reject the new organ. Modigraf is used to control your body's immune response enabling your body to accept the transplanted organ.

You may also be given Modigraf for an ongoing rejection of your transplanted liver, kidney, heart or other organ or if any previous treatment you were taking was unable to control this immune response after your transplantation.

Modigraf is used in adults and children.

2. What you need to know before you take Modigraf

Do not take Modigraf
- If you are allergic to tacrolimus or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to sirolimus (another substance used to prevent rejection of your transplanted organ) or to any macrolide antibiotic (e.g., erythromycin, clarithromycin, josamycin).

Warnings and precautions
Talk to your doctor or pharmacist before taking Modigraf

- if you have or have had liver problems.
- if you have diarrhoea for more than one day.
- if you feel strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting.
- if you have an alteration of the electrical activity of your heart called "QT prolongation".
- if you have or have had damage to the smallest blood vessels, known as thrombotic microangiopathy/thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome. Tell your doctor if you develop fever, bruising under the skin (which may appear as red dots), unexplained tiredness, confusion, yellowing of the skin or eyes, reduced urine output, vision

loss and seizures (see section 4). When tacrolimus is taken together with sirolimus or everolimus, the risk of developing these symptoms may increase.

Please avoid taking any herbal remedies, e.g., St. John's wort (*Hypericum perforatum*) or any other herbal products as this may affect the effectiveness and the dose of Modigraf that you need to receive. If in doubt please consult your doctor prior to taking any herbal products or remedies.

Your doctor may need to adjust your dose of Modigraf.

You should keep in regular contact with your doctor. From time to time, your doctor may need to do blood, urine, heart, eye tests, to set the right dose of Modigraf.

You should limit your exposure to the sun and UV (ultraviolet) light whilst taking Modigraf. This is because immunosuppressants like Modigraf could increase the risk of skin cancer. In case of sun exposure, wear appropriate protective clothing and use a sunscreen with a high sun protection factor.

Precaution for handling:
Direct contact with any part of your body like your skin or eyes, or breathing in of injection solutions, powder or granules contained in tacrolimus products should be avoided during preparation. If such contact occurs, wash the skin and eyes.

Other medicines and Modigraf
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is not recommended that Modigraf is taken with ciclosporin (another medicine used for the prevention of transplant organ rejection).

If you need to attend a doctor other than your transplant specialist, tell the doctor that you are taking tacrolimus. Your doctor may need to consult your transplant specialist if you should use another medicine that could increase or decrease your tacrolimus blood level.

Modigraf blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking Modigraf, which may require interruption, an increase or a decrease in Modigraf dose.

Some patients have experienced increases in tacrolimus blood levels while taking other medicines. This could lead to serious side effects, such as kidney problems, nervous system problems, and heart rhythm disturbances (see section 4).
An effect on the Modigraf blood levels may occur very soon after starting the use of another medicine, therefore frequent continued monitoring of your Modigraf blood level may be needed within the first few days of starting another medicine and frequently while treatment with the other medicine continues. Some other medicines may cause tacrolimus blood levels to decrease, which could increase the risk of rejecting the transplanted organ. In particular, you should tell your doctor if you are taking or have recently taken medicines like:
- antifungal medicines and antibiotics, particularly so-called macrolide antibiotics, used to treat infections e.g., ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole, clotrimazole, isavuconazole, miconazole, caspofungin, telithromycin, erythromycin, clarithromycin, josamycin, azithromycin, rifampicin, rifabutin, isoniazid and flucloxacillin
- letermovir, used to prevent illness caused by CMV (human cytomegalovirus)
- HIV protease inhibitors (e.g., ritonavir, nelfinavir, saquinavir), the booster medicine cobicistat, and combination tablets, or HIV non-nucleoside reverse transcriptase inhibitors (efavirenz, etravirine, nevirapine) used to treat HIV infection
- HCV protease inhibitors (e.g., telaprevir, boceprevir, the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir, elbasvir/grazoprevir, and glecaprevir/pibrentasvir), used to treat hepatitis C infection

- nilotinib and imatinib, idelalisib, ceritinib, crizotinib, apalutamide, enzalutamide, or mitotane (used to treat certain cancers)
- mycophenolic acid, used to suppress the immune system to prevent transplant rejection
- medicines for stomach ulcer and acid reflux (e.g., omeprazole, lansoprazole or cimetidine)
- antiemetics, used to treat nausea and vomiting (e.g., metoclopramide)
- cisapride or the antacid magnesium-aluminium-hydroxide, used to treat heartburn
- the contraceptive pill, hormone treatments with ethinylestradiol, or hormone treatments with danazol
- medicines used to treat high blood pressure or heart problems (e.g., nifedipine, nicardipine, diltiazem and verapamil)
- anti-arrhythmic medicines (amiodarone) used to control arrhythmia (uneven beating of the heart)
- medicines known as "statins" used to treat elevated cholesterol and triglycerides
- carbamazepine, phenytoin or phenobarbital, used to treat epilepsy
- metamizole, used to treat pain and fever
- the corticosteroids prednisolone and methylprednisolone, belonging to the class of corticosteroids used to treat inflammations or suppress the immune system (e.g., in transplant rejection)
- nefazodone, used to treat depression
- herbal preparations containing St. John's wort (*Hypericum perforatum*) or extracts of *Schisandra sphenanthera*.
- cannabidiol (uses amongst others include treatment of seizures)

Tell your doctor if you are receiving treatment for hepatitis C. The drug treatment for hepatitis C may change your liver function and may affect blood levels of tacrolimus. Tacrolimus blood levels may fall or may increase depending on the medicines prescribed for hepatitis C. Your doctor may need to closely monitor tacrolimus blood levels and make necessary adjustments of Modigraf dose after you start treatment for hepatitis C.

Tell your doctor if you are taking or need to take ibuprofen (used to treat fever, inflammation and pain), antibiotics (cotrimoxazole, vancomycin, or aminoglycoside antibiotics such as gentamicin), amphotericin B (used to treat fungal infections) or antivirals (used to treat viral infections e.g. acyclovir, ganciclovir, cidofovir, foscarnet). These may worsen kidney or nervous system problems when taken together with Modigraf.

Tell your doctor if you are taking sirolimus or everolimus. When tacrolimus is taken together with sirolimus or everolimus, the risk of developing thrombotic microangiopathy, thrombotic thrombocytopenic purpura, and haemolytic uraemic syndrome may increase (see section 4).

Your doctor also needs to know if you are taking potassium supplements or certain diuretics used for heart failure, hypertension and kidney disease, (e.g. amiloride, triamterene, or spironolactone), or the antibiotics trimethoprim or cotrimoxazole that may increase levels of potassium in your blood, non-steroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen) used for fever, inflammation and pain, anticoagulants (blood thinners), or oral medicines for diabetes, while you take Modigraf.

If you need to have any vaccinations, please tell your doctor before.

Modigraf with food and drink
You should generally take Modigraf on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal. Grapefruit and grapefruit juice should be avoided while taking Modigraf, since it can affect its levels in the blood.

Pregnancy and breast-feeding
If you take Modigraf during pregnancy, it may pass into your baby through the placenta. It could potentially influence the health of the baby or adversely influence the course of the pregnancy.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Modigraf passes into breast milk. Therefore, you should not breast-feed whilst using Modigraf.

Driving and using machines
Do not drive or use any tools or machines if you feel dizzy or sleepy, or have problems seeing clearly after taking Modigraf. These effects are more frequent if you also drink alcohol.

Modigraf contains lactose and sodium
Modigraf contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

3. How to take Modigraf

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Modigraf should be prescribed by doctors trained to treat transplant patients and experienced in the use of medicines that control the body's immune system (immunosuppressants).

Make sure that you receive the same tacrolimus medicine every time you collect your prescription, unless your transplant specialist has agreed to change to a different tacrolimus medicine.

This medicine should be taken twice a day. If the physical appearance has changed from the normal white granules, or if dose instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.

The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor calculated according to your body weight. Initial doses just after transplantation will generally be in the range of 0.075 - 0.30 mg per kg body weight per day depending on the transplanted organ. When treating rejection, these same doses may be used.

Your dose depends on your general condition and on which other immunosuppressive medicines you are taking.

Children and adolescents
Children and adolescents will receive doses of Modigraf calculated in the same way as adults. In general children need higher doses per kg of body weight to achieve the same effective levels in the blood as adults.

Following the initiation of your treatment with Modigraf, frequent blood tests will be taken by your doctor to define the correct dose and to adjust the dose from time to time. Your doctor will usually reduce your Modigraf dose once your condition has stabilised. Your doctor will tell you exactly how many sachets to take.

You will need to take Modigraf every day as long as you need immunosuppression to prevent rejection of your transplanted organ. You should keep in regular contact with your doctor.

Modigraf is taken orally twice daily, usually in the morning and evening. Take Modigraf on an empty stomach or 2 to 3 hours after a meal. Wait at least 1 hour until the next meal.

<u>How to prepare the Modigraf sachets for use?</u>
Your doctor will advise you on the number of sachets that you need to open and the volume of water that is required to make a suspension. For accurate measuring the volume of water you can use a syringe or graduated cylinder.

Pour the prescribed volume of water (at room temperature) into a glass or cup, up to a maximum of 50 ml. Place the cup with water on a stable surface. Do not use cups or spoons that are made of PVC (polyvinylchloride) to take Modigraf because the active substance in Modigraf may stick to PVC.

Carefully open the prescribed number of sachets, e.g. with a pair of scissors at the point indicated with an arrow. Hold the opened sachet between thumb and index finger above the cup with the open side of the sachet facing downwards. Gently tap on the closed end of the sachet and pour the contents of each sachet into the glass or cup containing the water. Do not use any utensils or liquids to empty the sachet. If you follow these instructions, you will get the right amount of granules from the sachet. It is normal that some granules stay behind; the sachet was designed that way.
Stir, or swirl gently until the granules have been suspended completely. The suspension can be drawn up with a syringe or swallowed directly by the patient. The liquid has a sweet taste. Rinse the glass or cup once with the same amount of water and drink this, too. The liquid should be drunk immediately after preparation.

If you take more Modigraf than you should
If you have accidentally taken too much Modigraf, contact your doctor or nearest hospital emergency department immediately.

If you forget to take Modigraf
Do not take a double dose to make up for forgotten individual doses.
If you have forgotten to take your Modigraf, wait until it is time for the next dose, and then continue as before.

If you stop taking Modigraf
Stopping your treatment with Modigraf may increase the risk of rejection of your transplanted organ. Do not stop your treatment unless your doctor tells you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Modigraf reduces your body's defense mechanism (immune system), which will not be as good at fighting infections. Therefore, you may be more prone to infections while you are taking Modigraf. Some infections could be serious or fatal and may include infections caused by bacteria, viruses, fungi, parasites, or other infections.
Tell your doctor immediately if you get signs of an infection including:
- Fever, cough, sore throat, feeling weak or generally unwell
- Memory loss, trouble thinking, difficulty walking or loss of vision - these may be due to a very rare, serious brain infection, which can be fatal (Progressive Multifocal Leukoencephalopathy or PML)

Severe effects may occur, including allergic and anaphylactic reactions (a very serious type of allergic reaction with fainting and difficulty breathing, which needs immediate medical attention). Benign and malignant tumours have been reported following Modigraf treatment.
Tell your doctor immediately if you have or suspect you may have any of the following serious side effects:

<u>Serious common side effects (may affect up to 1 in 10 people):</u>
- Gastrointestinal perforation: strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting.
- Insufficient function of your transplanted organ.
- Blurred vision.

<u>Serious uncommon side effects (may affect up to 1 in 100 people):</u>
- Thrombotic microangiopathy (damage to the smallest blood vessels) including haemolytic uraemic syndrome, a condition with the following symptoms: low or no urine output (acute renal failure), extreme tiredness, yellowing of the skin or eyes (jaundice) and abnormal bruising or bleeding and signs of infection.

Serious rare side effects (may affect up to 1 in 1,000 people):

- Thrombotic Thrombocytopenic Purpura: a condition involving damage to the smallest blood vessels and characterised by fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice), with symptoms of acute renal failure (low or no urine output), vision loss and seizures.
- Toxic epidermal necrolysis: erosion and blistering of skin or mucous membranes, red swollen skin that can detach in large parts of the body.
- Blindness.

Serious very rare side effects (may affect up to 1 in 10,000 people):

- Stevens-Johnson syndrome: unexplained widespread skin pain, facial swelling, serious illness with blistering of skin, mouth, eyes and genitals, hives, tongue swelling, red or purple skin rash that spreads, skin shedding.
- *Torsades de pointes*: change in the heart frequency that can be accompanied or not of symptoms, such as chest pain (angina), faint, vertigo or nausea, palpitations (feeling the heartbeat) and difficulty breathing.

Serious side effects - frequency not known (frequency cannot be estimated from the available data):

- Opportunistic infections (bacterial, fungal, viral and protozoal): prolonged diarrhea, fever and sore throat.
- Benign and malignant tumours have been reported following treatment as a result of immunosuppression.
- Cases of pure red cell aplasia (a very severe reduction in red blood cell counts), haemolytic anaemia (decreased number of red blood cells due to abnormal breakdown accompanied with tiredness) and febrile neutropenia (a decrease in the type of white blood cells which fight infection, accompanied by fever) have been reported. It is not known exactly how often these side effects occur. You may have no symptoms or depending on the severity of the condition, you may feel: fatigue, apathy, abnormal paleness of the skin (pallor), shortness of breath, dizziness, headache, chest pain and coldness in hands and feet.
- Cases of agranulocytosis (a severely lowered number of white blood cells accompanied with ulcers in the mouth, fever and infection(s)). You may have no symptoms or you may feel sudden fever, rigors and sore throat.
- Allergic and anaphylactic reactions with the following symptoms: a sudden itchy rash (hives), swelling of hands, feet, ankle, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and you may feel you are going to faint.
- Posterior Reversible Encephalopathy Syndrome (PRES): headache, confusion, mood changes, fits, and disturbances of your vision. These could be signs of a disorder known as posterior reversible encephalopathy syndrome, which has been reported in some patients treated with tacrolimus.
- Optic neuropathy (abnormality of the optic nerve): problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or restriction of your field of vision.

The side effects listed below may also occur after receiving Modigraf and could be serious:

Very common side effects (may affect more than 1 in 10 people):

- Increased blood sugar, diabetes mellitus, increased potassium in the blood
- Difficulty in sleeping
- Trembling, headache
- Increased blood pressure
- Liver function tests abnormal
- Diarrhoea, nausea
- Kidney problems

Common side effects (may affect up to 1 in 10 people):
- Reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts (seen in blood tests)
- Reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts (seen in blood tests)
- Anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare, hallucination, mental disorders
- Fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders
- Increased sensitivity to light, eye disorders
- Ringing sound in your ears
- Reduced blood flow in the heart vessels, faster heartbeat
- Bleeding, partial or complete blocking of blood vessels, reduced blood pressure
- Shortness in breath, changes in the lung tissue, collection of liquid around the lung, inflammation of the throat, cough, flu-like symptoms
- Inflammations or ulcers causing abdominal pain or diarrhoea, bleeding in the stomach, inflammations or ulcers in the mouth, collection of fluid in the belly, vomiting, abdominal pains, indigestion, constipation, flatulence, bloating, loose stools, stomach problems
- Bile duct disorders, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- Itching, rash, hair loss, acne, increased sweating
- Pain in joints, limbs, back and feet, muscle spasms
- Insufficient function of the kidneys, reduced production of urine, impaired or painful urination
- General weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling of temperature disturbed

Uncommon side effects (may affect up to 1 in 100 people):
- Changes in blood clotting, reduction in the number of all types of blood cells (seen in blood tests)
- Dehydration
- Reduced protein or sugar in the blood, increased phosphate in the blood
- Coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- Opacity of the eye lens
- Impaired hearing
- Irregular heartbeat, stop of heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, heart rate and pulse abnormal
- Blood clot in a vein of a limb, shock
- Difficulties in breathing, respiratory tract disorders, asthma
- Obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your throat, delayed emptying of the stomach
- Inflammation of the skin, burning sensation in the sunlight
- Joint disorders
- Inability to urinate, painful menstruation and abnormal menstrual bleeding
- Multiple organ failure, flu-like illness, increased sensitivity to heat and cold, feeling of pressure on your chest, jittery or abnormal feeling, increase of the enzyme lactate dehydrogenase in your blood, weight loss

Rare side effects (may affect up to 1 in 1,000 people):
- Small bleedings in your skin due to blood clots
- Increased muscle stiffness
- Deafness
- Collection of fluid around the heart
- Acute breathlessness
- Cyst formation in your pancreas

- Problems with blood flow in the liver
- Increased hairiness
- Thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer

Very rare side effects (may affect up to 1 in 10,000 people):
- Muscular weakness
- Abnormal heart scan
- Liver failure
- Painful urination with blood in the urine
- Increase of fat tissue

Children and adolescents
Children and adolescents may experience the same side effects as adults.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Modigraf

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and sachet after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

After preparation, the suspension should be taken immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Modigraf contains
- The active substance is tacrolimus.
  Each sachet of Modigraf 0.2 mg granules contains 0.2 mg of tacrolimus (as monohydrate).
  Each sachet of Modigraf 1 mg granules contains 1 mg of tacrolimus (as monohydrate).
- The other ingredients are: lactose monohydrate, hypromellose (E464) and croscarmellose sodium (E468).

What Modigraf looks like and contents of the pack
Modigraf granules for oral suspension are white granules supplied in sachets.
Packs containing 50 sachets are available.

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Sylviusweg 62
2333 BE Leiden
Netherlands

Manufacturer
Astellas Ireland Co. Ltd.
Killorglin

County Kerry, V93FC86
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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