

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 and other malignancies, including skin cancers and Kaposi's sarcoma (see section 4.8).

A combination of immunosuppressives such as antilymphocytic antibodies (e.g. basiliximab, daclizumab) given concomitantly increases the risk of EBV-associated lymphoproliferative disorders. EBV-Viral Capsid Antigen (VCA)-negative patients have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with 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.

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

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

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

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 thrombocytopenic 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) <i>[see section 4.4]</i> .	Avoid grapefruit or grapefruit juice.
Ciclosporin	May increase tacrolimus whole blood trough concentrations. In addition, synergistic/additive nephrotoxic effects can occur.	The simultaneous use of ciclosporin and tacrolimus should be avoided <i>[see section 4.4]</i> .
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 <i>[see section 4.4]</i> . 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.	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
	The effect on tacrolimus blood concentrations may remain for several days after co-administration is completed.	
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 <i>Schisandra sphenanthera</i>	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.
<i>In vitro</i> the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephentyoin, 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 (<i>Hypericum perforatum</i>)	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

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
		dose may need to be adjusted gradually. Monitor graft function closely.
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 <i>[see section 4.4]</i> .	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed <i>[see section 4.2]</i> . 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 <i>[see section 4.2]</i> . 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 <i>[see sections 4.2 and 4.4]</i> .
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 <i>[see section 4.2]</i> .
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 <i>[see section 4.2]</i> . 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 <i>[see section 4.4]</i> .	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed <i>[see section 4.2]</i> . 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.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Direct-acting antiviral (DAA) therapy	May have impact on the pharmacokinetics of tacrolimus by changes in liver function during DAA therapy, related to clearance of 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.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed to ensure continued efficacy and safety.

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

Data from women show that tacrolimus crosses the placenta. There is a risk for hyperkalaemia in the newborn (e.g. incidence in neonates of 7.2%, i.e., 8 of 111) which tends to normalise spontaneously. 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).

Results from a non-interventional post-authorisation safety study [EUPAS37025]

A post-authorisation safety study analysed 2,905 pregnancies from the Transplant Pregnancy Registry International (TPRI), assessing outcomes in women treated with tacrolimus (383 reported prospectively, including 247 kidney and 136 liver transplant patients), and those on other immunosuppressants. Based on limited data (289 prospectively-reported pregnancies with 1st trimester tacrolimus exposure), study results did not indicate an increased risk of major malformations. A higher prevalence of spontaneous abortion was observed among women treated with tacrolimus compared with alternative immunosuppressants. Among kidney transplant patients there was also a higher prevalence of pre-eclampsia in women treated with tacrolimus. However, overall, there were insufficient evidence to conclude on the risk of these outcomes. Among kidney and liver transplant patients exposed to tacrolimus, 45%-55% of their live births were premature, with 75%-85% having a normal birth weight for gestational age. Similar results were observed for other immunosuppressants, although conclusions were hindered by limited evidence.

In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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, skin malignancies and Kaposi's sarcoma 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
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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:	hyposacusis
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:	<i>Torsades de pointes</i>

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.

Ireland

HPRA Pharmacovigilance

Website: www.hpra.ie

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.

Biotransformation

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.

Elimination

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 $26\% \pm 23\%$ (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 terephthalate (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

14/02/2025

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