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).
Each sachet contains less than 1 mmol sodium (23 mg).

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).
Each sachet contains less than 1 mmol sodium (23 mg).

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.

When substances with a potential for interaction (see section 4.5) – particularly strong inhibitors of CYP3A4 (such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers of CYP3A4 (such as rifampicin, rifabutin) – are being combined with tacrolimus, tacrolimus blood levels should be monitored to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure.

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).

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 nephrotoxic or neurotoxic effects may increase the risks of these effects (see section 4.5).

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.

<u>Gastrointestinal disorders</u>
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.

<u>Cardiac disorders</u>
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 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 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.

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
Modigraf granules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels.

It is strongly recommended to closely monitor tacrolimus blood levels, as well as, QT prolongation (with ECG), renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly, and to interrupt or adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels
Clinically the following substances have been shown to increase tacrolimus blood levels:
Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole, voriconazole, and isavuconazole, the macrolide antibiotic erythromycin, 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), or the CMV antiviral letermovir, the pharmacokinetic enhancer cobicistat, and the tyrosine kinase inhibitors nilotinib and imatinib. Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients.
Pharmacokinetics studies have indicated that the increase in blood levels 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.
Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, amiodarone, danazol, ethinylestradiol, omeprazole, nefazodone and (Chinese) herbal remedies containing extracts of *Schisandra sphenanthera*.
In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen, troleandomycin.
Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.
Lansoprazole and ciclosporin may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

Other interactions potentially leading to increased tacrolimus blood levels
Tacrolimus is extensively bound to plasma proteins. Possible interactions with other medicinal products known to have high affinity for plasma proteins should be considered (e.g., NSAIDs, oral anticoagulants, or oral antidiabetics).
Other potential interactions that may increase systemic exposure of tacrolimus include prokinetic agents (such as metoclopramide and cisapride), cimetidine and magnesium-aluminium-hydroxide.

CYP3A4 inducers potentially leading to decreased tacrolimus blood levels
Clinically the following substances have been shown to decrease tacrolimus blood levels:
Strong interactions have been observed with rifampicin, phenytoin or St. John's Wort (*Hypericum perforatum*) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.

High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels.
Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

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.

Other interactions which have led to clinically detrimental effects
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole+trimethoprim, NSAIDs, ganciclovir or aciclovir).
Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.

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).

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 groupingadverse 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 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 (inl. 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
rare:	thrombotic thrombocytopenic purpura, hypoprothrombinaemia, thrombotic microangiopathy
not known:	pure red cell aplasia, agranulocytosis, haemolytic anaemia

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

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

not known: febrile neutropenia

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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.

Metabolism
Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4. 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

No special requirements.

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

September 2019.

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