

## NAME OF THE MEDICINAL PRODUCT

ADVAGRAF® 0.5 mg prolonged-release hard capsules

ADVAGRAF® 1 mg prolonged-release hard capsules

ADVAGRAF® 5 mg prolonged-release hard capsules

## QUALITATIVE AND QUANTITATIVE COMPOSITION

Prolonged-release hard capsule containing 0.5 mg, 1 mg and 5 mg tacrolimus on anhydrous basis (as 0.51 mg, 1.02 mg and 5.10 mg tacrolimus as monohydrate).

## PRODUCT DESCRIPTION

Advagraf 0.5 mg prolonged-release hard capsules are hard gelatin capsules imprinted in red with “0.5 mg” on the light yellow capsule cap and “647” on the orange capsule body, containing white powder. Advagraf 0.5 mg is supplied in blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 50 prolonged-release capsules are available.

Advagraf 1 mg prolonged-release hard capsules are hard gelatin capsules imprinted in red with “1 mg” on the white capsule cap and “677” on the orange capsule body, containing white powder. Advagraf 1 mg is supplied in blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 50 prolonged-release capsules are available.

Advagraf 5 mg prolonged-release hard capsules are hard gelatin capsules imprinted in red with “5 mg” on the greyish red capsule cap and “687” on the orange capsule body, containing white powder. Advagraf 5 mg is supplied in blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 50 prolonged-release hard capsules are available.

## CLINICAL PARTICULARS

### Therapeutic Indications

Prophylaxis of transplant rejection in adult kidney or liver allograft recipients.

Treatment of kidney or liver allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.

### Posology and Method of Administration

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

Inadvertent, unintentional or unsupervised switching of immediate- or prolonged-release formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of adverse reactions, including under- or over-immunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist (*see sections **Special warnings and precautions for use** and **Undesirable effects***). Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

### Posology

The recommended initial doses presented below are intended to act solely as a guideline. Advagraf 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. Advagraf dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring (see below under “Therapeutic drug monitoring”).

If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.

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

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

#### Prophylaxis of kidney transplant rejection

Advagraf therapy should commence at a dose of 0.20-0.30 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery.

Advagraf doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to Advagraf monotherapy. Post-transplant changes in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

#### Prophylaxis of liver transplant rejection

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

#### Conversion of Prograf-treated patients to Advagraf

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

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

#### Conversion from ciclosporin to tacrolimus

Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy (see sections **Special warnings and precautions for use** and **Interaction with other medicinal products and other forms of interaction**). The combined administration of ciclosporin and tacrolimus is not recommended. Advagraf therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, tacrolimus-based therapy has been initiated 12-24 hours after

discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected.

#### Treatment of allograft rejection

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

#### *Treatment of allograft rejection after kidney or liver transplantation*

For conversion from other immunosuppressants to once daily Advagraf, treatment should begin with the initial oral dose recommended in kidney and liver transplantation respectively for prophylaxis of transplant rejection.

#### 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<sub>24</sub>) and systemic exposure (AUC<sub>0-24</sub>) is similar between the two formulations Advagraf and Prograf.

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

Data from clinical studies suggest that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/mL. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels. In clinical practice, whole blood trough levels have generally been in the range 5-20 ng/mL in liver transplant recipients and 10-20 ng/mL in kidney transplant patients in the early post-transplant period. During subsequent maintenance therapy, blood concentrations have generally been in the range of 5-15 ng/mL in liver and kidney transplant recipients.

#### Special populations

##### *Hepatic impairment*

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

##### *Renal impairment*

As the pharmacokinetics of tacrolimus are unaffected by renal function (*see section **Pharmacokinetic properties***), 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.

#### *Older peoples*

There is no evidence currently available to indicate that dosing should be adjusted in older people.

#### *Paediatric patients*

The safety and efficacy of Advagraf in children under 18 years of age have not yet been established. Limited data are available but no recommendation on a posology can be made.

#### Method of administration

Advagraf is a once-a-day oral formulation of tacrolimus. It is recommended that the oral daily dose of Advagraf be administered once daily in the morning. Advagraf prolonged-release hard capsules should be taken immediately following removal from the blister. Patients should be advised not to swallow the desiccant. The capsules should be swallowed **whole** with fluid (preferably water). Advagraf 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 **Pharmacokinetic properties***). A forgotten morning dose should be taken as soon as possible on the same day. A double dose should not be taken on the next morning.

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

#### **Contraindications**

Hypersensitivity to tacrolimus, or to any of the excipients (*see section **List of excipients***).

Hypersensitivity to other macrolides.

#### **Special Warnings and Precautions for Use**

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under- or over- exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist (*see sections **Posology and method of administration** and **Undesirable effects***).

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

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

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 ***Interaction with other medicinal products and other forms of interaction***).

##### *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. When concomitant use of strong CYP3A4 inhibitors (such as ritonavir, cobicistat, ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin or josamycin) with tacrolimus is required, tacrolimus blood levels should be monitored frequently, starting within the first few days of coadministration, 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 ***Interaction with other medicinal products and other forms of interaction***).

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. When concomitant use of strong CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine) with tacrolimus is required, tacrolimus blood levels should be monitored frequently, starting within the first few days of coadministration, 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 ***Interaction with other medicinal products and other forms of interaction***).

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 ***Interaction with other medicinal products and other forms of interaction***).

##### *Herbal preparations*

Herbal preparations containing St. John's wort (*Hypericum perforatum*) should be avoided when taking Advagraf due to the risk of interactions that lead to a decrease in both blood concentrations and the therapeutic effect of tacrolimus (see section ***Interaction with other medicinal products and other forms of interaction***).

##### *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 ***Posology and method of administration*** and ***Interaction with other medicinal products and other forms of interaction***).

High potassium intake or potassium-sparing diuretics should be avoided (see section ***Interaction with other medicinal products and other forms of interaction***).

Certain combinations of tacrolimus with drugs known to have neurotoxic effects may increase the risk of these effects (see section ***Interaction with other medicinal products and other forms of interaction***).

#### 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 ***Interaction with other medicinal products and other forms of interaction***). 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.

#### Pure Red Cell Aphasia

Cases of pure red cell aphasia (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.

#### Cardiac disorders

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed in Prograf treated patients on rare occasions and may also occur with Advagraf. 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 preexisting heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g., initially at 3 months and then at 9 - 12 months). If abnormalities develop, dose reduction of Advagraf, 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 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 ***Interaction with other medicinal products and other forms of interaction***).

#### 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 ***Undesirable effects***).

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 Advagraf. 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 Advagraf are at increased risk for 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.

#### 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).

#### 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 **Posology and method of administration***).

### Excipients

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

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

### **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 **Posology and method of administration** and **Special warnings and precautions for use***). 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 <b>Special warnings and precautions for use</b></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 <b>Special warnings and precautions for use</b></i> ]. |

| Drug/Substance Class or Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Drug interaction effect                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Recommendations concerning co-administration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Products known to have nephrotoxic or neurotoxic effects:<br/>aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole + trimethoprim, NSAIDs, ganciclovir, acyclovir, amphotericin B, ibuprofen, cidofovir, foscarnet</p>                                                                                                                                                                                                                                                                                                                                                                                              | <p>May enhance nephrotoxic or neurotoxic effects of tacrolimus.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <p>When co-administration is required, monitor renal function and other side effects and adjust tacrolimus dose if needed.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p>Strong CYP3A4 inhibitors: antifungal agents (e.g., ketoconazole, 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.</p> | <p>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 <b>Special warnings and precautions for use</b>]</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 &gt;5 fold. When ritonavir combinations are co-administered, tacrolimus exposure may increase &gt;50 fold. Nearly all patients may require a reduction in tacrolimus dose and temporary interruption of tacrolimus may also be necessary. The effect on tacrolimus blood concentrations may remain for several days after co-administration is completed.</p> | <p>When co-administration of a strong CYP3A4 inhibitor is required, 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.</p> |

| Drug/Substance Class or Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Drug interaction effect                                                                                                                                                                                                                                                                                                                          | Recommendations concerning co-administration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Moderate or weak CYP3A4 inhibitors:<br/>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></p> | <p>May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see section <b><i>Special warnings and precautions for use</i></b>]. A rapid increase in tacrolimus level may occur.</p>                                                                 | <p>Monitor tacrolimus whole blood trough concentrations frequently, starting within the first few days of co-administration. Reduce tacrolimus dose if needed [see section <b><i>Posology and method of administration</i></b>]. Monitor renal function, ECG for QT prolongation, and other side effects closely.</p>                                                                                                                                                                                                                                       |
| <p><i>In vitro</i> the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephénytoin, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen.</p>                                                                                                                                                                                                                                                                                                                          | <p>May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see section <b><i>Special warnings and precautions for use</i></b>].</p>                                                                                                                 | <p>Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed [see section <b><i>Posology and method of administration</i></b>]. Monitor renal function, ECG for QT prolongation, and other side effects closely.</p>                                                                                                                                                                                                                                                                                                        |
| <p>Strong CYP3A4 inducers: rifampicin, phenytoin carbamazepine, apalutamide, enzalutamide, mitotane, or St. John's wort (<i>Hypericum perforatum</i>)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                     | <p>May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection [see section <b><i>Special warnings and precautions for use</i></b>]. Maximal effect on tacrolimus blood concentrations may be achieved 1-2 weeks after coadministration. The effect may remain 1-2 weeks after completion of the treatment.</p> | <p>When co-administration of a strong CYP3A4 inducer is required, patients may require an increase in tacrolimus dose. Changes in tacrolimus dose should be individualized and adjusted as needed based on tacrolimus trough concentrations, which should be assessed at initiation, monitored frequently throughout (starting within the first few days) and re-evaluated on and after completion of the CYP3A4 inducer. After use of the CYP3A4 inducer has ended, tacrolimus dose may need to be adjusted gradually. Monitor graft function closely.</p> |
| <p>Moderate CYP3A4 inducers: metamazole, phenobarbital, isoniazid, rifabutin, efavirenz, etravirine, nevirapine; weak CYP3A4 inducers: flucloxacillin</p>                                                                                                                                                                                                                                                                                                                                                                                                                                     | <p>May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection [see section <b><i>Special warnings and precautions for use</i></b>].</p>                                                                                                                                                                        | <p>Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed [see section <b><i>Posology and method of administration</i></b>]. Monitor graft function closely.</p>                                                                                                                                                                                                                                                                                                                                                       |

| Drug/Substance Class or Name                                                                                    | Drug interaction effect                                                                                                                                                                                                                                                                                                         | Recommendations concerning co-administration                                                                                                                                                                                                                                                                            |
|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Caspofungin                                                                                                     | May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection. Mechanism of interaction has not been confirmed.                                                                                                                                                                                  | Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed [see section <b>Posology and method of administration</b> ]. Monitor graft function closely.                                                                                                                                |
| Cannabidiol (P-gp inhibitor)                                                                                    | There have been reports of increased tacrolimus blood levels during concomitant use of tacrolimus with cannabidiol. This may be due to inhibition of intestinal P-glycoprotein, leading to increased bioavailability of tacrolimus.                                                                                             | Tacrolimus and cannabidiol should be co-administered with caution, closely monitoring for side effects. Monitor tacrolimus whole blood trough concentrations and adjust the tacrolimus dose if needed [see sections <b>Posology and method of administration</b> and <b>Special warnings and precautions for use</b> ]. |
| Products known to have high affinity for plasma proteins, e.g., NSAIDs, oral anticoagulants, oral antidiabetics | Tacrolimus is extensively bound to plasma proteins. Possible interactions with other active substances known to have high affinity for plasma proteins should be considered.                                                                                                                                                    | Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed [see section <b>Posology and method of administration</b> ].                                                                                                                                                                  |
| Prokinetic agents: metoclopramide, cimetidine and magnesium-aluminium-hydroxide                                 | May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation).                                                                                                                                                                            | Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed [see section <b>Posology and method of administration</b> ]. Monitor closely for renal function, for QT prolongation with ECG, and for other side effects.                                                                    |
| Maintenance doses of corticosteroids                                                                            | May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection [see section <b>Special warnings and precautions for use</b> ].                                                                                                                                                                    | Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed [see section <b>Posology and method of administration</b> ]. Monitor graft function closely.                                                                                                                                |
| High dose prednisolone or methylprednisolone                                                                    | May have impact on tacrolimus blood levels (increase or decrease) when administered for the treatment of acute rejection.                                                                                                                                                                                                       | Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed.                                                                                                                                                                                                                              |
| Direct-acting antiviral (DAA) therapy                                                                           | May have impact on the pharmacokinetics of tacrolimus by changes in liver function during DAA therapy, related to clearance of hepatitis virus. A decrease in tacrolimus blood levels may occur. However, the CYP3A4 inhibiting potential of some DAAs may counteract that effect or lead to increased tacrolimus blood levels. | Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed to ensure continued efficacy and safety.                                                                                                                                                                                      |

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 **Special warnings and precautions for use***).

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 **Special warnings and precautions for use***). 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 **Posology and method of administration** and **Special warnings and precautions for use***).

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

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

Limited knowledge of interactions between tacrolimus and statins is available. Clinical data suggest that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus. Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine.

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

Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided (*see section **Special warnings and precautions for use***).

### **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 1<sup>st</sup> 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 was 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 **Preclinical safety data***).

#### *Breast-feeding*

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

#### *Fertility*

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

#### **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 (Advagraf) on the ability to drive and use machines have been performed.

#### **Undesirable Effects**

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

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

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, undesirable effects 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 Advagraf.

#### 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*

***Special warnings and precautions for use).***

Endocrine disorders

rare: hirsutism

Metabolism and nutrition disorders

very common: diabetes mellitus, hyperglycaemic conditions, hyperkalaemia

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

uncommon: dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia

Psychiatric disorders

very common: insomnia

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

uncommon: psychotic disorder

Nervous system disorders

very common: headache, tremor

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

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

rare: hypertonia

very rare: myasthenia

not known: posterior reversible encephalopathy syndrome (PRES)

Eye disorders

common: eye disorders, vision blurred, photophobia

uncommon: cataract

rare: blindness

not known: optic neuropathy

Ear and labyrinth disorders

common: tinnitus

uncommon: hypoacusis

rare: deafness neurosensory

very rare: hearing impaired

Cardiac disorders

common: ischaemic coronary artery disorders, tachycardia

uncommon: heart failures, ventricular arrhythmias and cardiac arrest, supraventricular arrhythmias, cardiomyopathies, ECG investigations abnormal, ventricular hypertrophy, palpitations, heart rate and pulse investigations abnormal

rare: pericardial effusion

very rare: echocardiogram abnormal, electrocardiogram QT prolonged, *Torsades de pointes*

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, amylase increased, ileus paralytic, gastrooesophageal reflux disease, impaired gastric emptying

rare: pancreatic pseudocyst, subileus

#### Hepatobiliary disorders

very common: liver function tests abnormal

common: bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice

rare: venoocclusive liver disease, hepatic artery thrombosis

very rare: hepatic failure

#### 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, blood alkaline phosphatase increased, weight increased

uncommon: weight decreased, influenza like illness, blood lactate dehydrogenase increased,

feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance  
rare: fall, ulcer, chest tightness  
very rare: fat tissue increased

#### Injury, poisoning and procedural complications

common: primary graft dysfunction

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

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

#### **Overdose**

Experience with overdose is limited. Several cases of accidental overdose have been reported with tacrolimus; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy and increases in blood urea nitrogen, serum creatinine and alanine aminotransferase levels.

No specific antidote to tacrolimus therapy is available. If overdose occurs, general supportive measures and symptomatic treatment should be conducted.

Based on its high molecular weight, poor aqueous solubility, and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus will not be dialysable. 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.

### **PHARMACOLOGICAL PROPERTIES**

#### **Pharmacodynamic Properties**

Pharmacotherapeutic group: Immunosuppressants calcineurin inhibitors, ATC code: L04AD02

#### Mechanism of action

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 cytokine 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  $\gamma$ -interferon) and the expression of the interleukin-2 receptor.

#### Results from clinical trials performed with once-daily tacrolimus Advagraf

##### Liver transplantation

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

##### Kidney transplantation

The efficacy and safety of Advagraf and Prograf, both in combination with mycophenolate mofetil

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

The efficacy and safety of Prograf, ciclosporin and Advagraf, all in combination with basiliximab antibody induction, MMF and corticosteroids, was compared in 638 *de novo* kidney transplant recipients. The incidence of efficacy failure at 12 months (defined as death, graft loss, biopsy-confirmed acute rejection, or lost to follow-up) was 14.0% in the Advagraf group (N=214), 15.1% in the Prograf group (N=212) and 17.0% in the ciclosporin group (N=212). The treatment difference was -3.0% (Advagraf-ciclosporin) (95.2% confidence interval [-9.9%, 4.0%]) for Advagraf vs. ciclosporin and -1.9% (Prograf-ciclosporin) (95.2% confidence interval [-8.9%, 5.2%]) for Prograf vs. ciclosporin. The 12-month patient survival rates were 98.6% for Advagraf, 95.7% for Prograf and 97.6% for ciclosporin; in the Advagraf arm 3 patients died (all male), in the Prograf arm 10 patients died (3 female, 7 male) and in the ciclosporin arm 6 patients died (3 female, 3 male). 12-month graft survival was 96.7% for Advagraf, 92.9% for Prograf and 95.7% for ciclosporin.

## **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. Advagraf is a prolonged-release formulation of tacrolimus resulting in an extended oral absorption profile with an average time to maximum blood concentration ( $C_{max}$ ) of approximately 2 hours ( $t_{max}$ ).

Absorption is variable and the mean oral bioavailability of tacrolimus (investigated with the Prograf formulation) is in the range of 20%-25% (individual range in adult patients 6%-43%). The oral bioavailability of Advagraf was reduced when it was administered after a meal. Both the rate and extent of absorption of Advagraf were reduced when administered with food.

Bile flow does not influence the absorption of tacrolimus and therefore treatment with Advagraf may commence orally.

A strong correlation exists between AUC and whole blood trough levels at steady-state for Advagraf. 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  $\alpha$ -1-acid glycoprotein.

Tacrolimus is extensively distributed in the body. The steady-state volume of distribution based on plasma concentrations is approximately 1300 L (healthy subjects). Corresponding data based on whole blood averaged 47.6 L.

### Metabolism

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

### Excretion

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance estimated from whole blood concentrations was 2.25 L/h. In adult liver and kidney transplant patients, values of

4.1 L/h and 6.7 L/h, respectively, have been observed. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of tacrolimus, or corticosteroid-induced increased metabolism, are considered to be responsible for the higher clearance rates observed following transplantation.

The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood is approximately 43 hours.

Following intravenous and oral administration of <sup>14</sup>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.

### **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 ng/mL which is more than 6-fold higher than mean peak concentrations observed with Advagraf in clinical transplantation.

Embryofetal 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.

### **List of excipients**

Capsule content Hypromellose Ethylcellulose Lactose monohydrate Magnesium stearate

#### Capsule shell

Titanium dioxide (E171) Yellow iron oxide (E172) Red iron oxide (E172) Sodium laurilsulfate Gelatine

#### Printing ink (Opacode S-1-15083) Shellac

Lecithin (soya) Simeticone

Red iron oxide (E172) Hydroxypropylcellulose

### **Incompatibilities**

Tacrolimus is not compatible with PVC (polyvinylchloride). Tubing, syringes and other equipment used to prepare or administer a suspension of Advagraf capsule contents should not contain PVC.

### **Shelf Life**

3 years

After opening the aluminium pouch: 1 year

### **Special Precautions for Storage**

Do not store above 30°C. Store in the original package in order to protect from moisture. Keep out of reach of children.

### **How supplied**

Transparent PVC/PVDC aluminium blister wrapped in an aluminium pouch with a desiccant containing 10 capsules per blister.

Pack size: 50 prolonged-release hard capsules.

**Instructions for Use and Handling and Disposal**

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

**Source of gelatin**

Bovine

**MANUFACTURED BY**

Astellas Ireland Co. Ltd  
Killorglin, Co. Kerry.  
V93 FC86, Ireland.

**DATE OF REVISION OF THE TEXT**

CCDSv8.0/9.0 (09 Sep 2025)

For any enquiry, please write to [pv.my@astellas.com](mailto:pv.my@astellas.com).