PROGRAF™, ADVAGRAF™, MODIGRAF™ (TACROLIMUS)

Public Risk Management Plan (RMP) Summary

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Prograf/Advagraf/Modigraf is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Prograf/Advagraf/Modigraf in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Astellas Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Prograf/Advagraf/Modigraf.

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

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Summary of risk management plan for Prograf™, Advagraf™, Modigraf™ (Systemic Tacrolimus)

This is a summary of the RMP for Prograf™, Advagraf™, and Modigraf™. The RMP details important risks of Prograf, Advagraf, and Modigraf, how these risks can be minimized, and how more information will be obtained about these risks and uncertainties (missing information).

Prograf, Advagraf, and Modigraf SmPCs and its package leaflets, give essential information to healthcare professionals and patients on how it should be used.

In the EU, Prograf capsules and concentrate for infusion are authorized via mutual recognition procedure/national procedures; consequently, there is no European Public Assessment Report (EPAR) for Prograf.

Advagraf and Modigraf are authorized via centralized procedures.

This summary of the RMP for Prograf, Advagraf and Modigraf should be read in the context of all this information, including, for the centrally authorized products Advagraf and Modigraf, the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Prograf, Advagraf, and Modigraf's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Prograf is authorized for prophylaxis of transplant rejection in liver, kidney or heart allograft recipients; and for the treatment of allograft rejection, resistant to treatment with other immunosuppressive medicinal products (see SmPC for the full indication). It contains tacrolimus monohydrate as the active substance, and it is given orally or is available as a concentrate solution for infusion.

Advagraf is authorized for prophylaxis of transplant rejection in adult kidney or liver allograft recipients; and for the treatment of allograft rejection, resistant to treatment with other immunosuppressive medicinal products in adult patients (refer to SmPC for the full indication). It contains tacrolimus monohydrate as the active substance, and it is given orally.

Modigraf is authorized for prophylaxis of transplant rejection in liver, kidney or heart allograft recipients; and for the treatment of allograft rejection, resistant to treatment with other immunosuppressive medicinal products (see SmPC for the full indication). It contains tacrolimus monohydrate as the active substance, and it is given orally.

Further information about the evaluation of the centrally authorized products Advagraf and Modigraf benefits can be found in Advagraf's and Modigraf's EPARs, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/advagraf and https://www.ema.europa.eu/en/medicines/human/EPAR/modigraf.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Prograf, Advagraf, and Modigraf, together with measures to minimize such risks and the proposed studies for learning more about Prograf, Advagraf, and Modigraf's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and the SmPC, addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen as to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute the routine risk minimization measures.

In addition to these measures, information about the adverse reactions is collected continuously and is regularly analyzed, including PSUR assessment, so that immediate action can be taken if necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Prograf, Advagraf, and Modigraf are those risks that need special risk management activities to further investigate or minimize them, so that the medicinal product can be safely administered or taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Prograf, Advagraf, and Modigraf. Potential risks are concerns for which an association with the use of this medicine is possible, based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information regarding the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Malignant neoplasms • Serious infections and reactivation of pre-existing infections • Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences • Interaction with other medication and herbal drugs • Ventricular hypertrophy • Cardiomyopathies • Use during pregnancy • Use during lactation
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important Identified risk: Malignant neoplasms	
Evidence for linking the risk to the medicine	The increased risk in transplant recipients for developing cancer has been well described in the literature and Clinical Practice Guidelines and is also based on data from tacrolimus post-marketing experience.
Risk factors and risk groups	Risk factors for posttransplant malignancy include traditional risk factors such as advancing age, smoking, drinking alcohol, obesity, sun exposure, and family history, and risk factors that are unique to the transplant population, including immunosuppression, oncogenic viral infections, and disease-specific associations (e.g., factors related to end-stage organ disease or dialysis in the case of kidney transplant recipients) [Rossi and Klein, 2019; Acuna, 2018].
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • SmPC Section 4.4 in which a warning is included that concomitant use of tacrolimus and anti-lymphocyte treatment increases the risk of Epstein-Barr-Virus (EBV)-associated lymphoproliferative disorders. • SmPC Section 4.4 in which recommendations are given to limit the exposure to sunlight • SmPC Section 4.4 in which a recommendation is given to ascertain, in EBV- Viral Capsid Antigen (VCA)-negative patients, EBV-VCA serology before initiation of tacrolimus therapy and a recommendation for careful monitoring with EBV-PCR • PL Sections 2 and 4 Additional risk minimization measures:

Important Identified risk: Malignant neoplasms	
	• None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

EBV: Epstein-Barr-Virus; PL: Package Leaflet; PCR: Polymerase Chain Reaction; SmPC: Summary of Product Characteristics; VCA: Viral Capsid Antigen

Important Identified risk: Serious infections and reactivation of pre-existing infections	
Evidence for linking the risk to the medicine	This important identified risk has been well described in the literature and Clinical Practice Guidelines and is also based on data from tacrolimus post-marketing experience.
Risk factors and risk groups	Increased risk and severity of infection in kidney transplant recipients are explained by many factors, including the recipient's condition, such as surgical complications, or the use of indwelling catheters; the possibility of transmission of infection from donor to recipient; overimmunosuppression; active smoking; and obesity, etc. Viral infections in kidney transplant recipients, which occur more frequently during the first few months, are most likely in the context of greater immunosuppression. Furthermore, recipient age is often a significant risk factor for bacterial infections, but not viral/fungal infections. Type of immunosuppressive agent such as use of induction therapy with antithymocyte globulin is also associated with viral infection. The relationship between bacterial infection in kidney transplant recipients and overimmunosuppression is well established. However, in many cases, there are additional identifiable risk factors for bacterial infection, including surgical complications, intravenous or urinary catheters, urinary retention or vesicoureteral reflux. Patients with a tuberculin purified protein derivative-positive skin test or a positive IFN-γ release assay for tuberculosis before transplantation are also at increased risk of *Mycobacterium tuberculosis* infection after transplantation [Neuberger, 2017].
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • SmPC Section 4.4 including a warning in SmPC Section 4.4 about the increased risk for serious infections or reactivation of infections, often related to a high total immunosuppressive burden, which may lead to serious or fatal conditions. • SmPC Section 4.4 in which the recommendation is given to consider, in the differential diagnosis in immunosuppressed patients with deteriorating hepatic or renal function or neurological symptoms, that these conditions may be associated with serious infections or reactivation of infections.

Important Identified risk: Serious infections and reactivation of pre-existing infections	
	• SmPC Section 4.4 in which the recommendation is given for prevention and management of infections in accordance with appropriate clinical guidance. • SmPC Section 4.9 in which recommendations are given in case of accidental overdose. • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

IFN: Interferon; PL: Package Leaflet; SmPC: Summary of Product Characteristics

Important Identified risk: Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences	
Evidence for linking the risk to the medicine	This important identified risk is based on data from tacrolimus post-marketing experience.
Risk factors and risk groups	A systematic review was published in 2018; this review investigated the epidemiology of medication errors and error-related adverse events in adults, in primary care, ambulatory care and patients' homes. Risk factors for medication errors listed in this 2018 review, related to patients, healthcare professionals and/or medications are listed below [Assiri et al, 2018]. Patient related risk factors for the development of medication errors: polypharmacy, increased age, number of diseases or comorbidities, female gender, low level of education, hospital admission and middle family income. Risk factors related to healthcare professionals for the development of medication errors: more than one physician involved in their care, general practice (GP), age ≥51 years, male GP, frequent changes in prescription, not considering the prescription of other physicians, inconsistency in the information and outpatient clinic visits Medication related risk factors for the development of medication errors: multiple medication storage locations used, expired medication present, discontinued medication repeats retained, hoarding of medications, therapeutic duplication, no medication administration routine, poor adherence and patients confused by generic and trade names.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.2 and 4.8 • SmPC Section 4.4, in which medication errors are addressed and recommendations are given to maintain patients on a

Important Identified risk: Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences	
	single formulation of tacrolimus and to alter formulations or regimen only under the close supervision of a transplant specialist • SmPC Section 4.2 in which recommendations are given about the need for therapeutic drug monitoring and dose adjustments following conversion to any alternative formulation. • PL Section 3 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

GP: General Practice; PL: Package Leaflet; SmPC: Summary of Product Characteristics

Important Identified risk: Interaction with other medication and herbal drugs	
Evidence for linking the risk to the medicine	This important identified risk has been well described in drug interaction studies, literature and is also based on data from tacrolimus post-marketing experience.
Risk factors and risk groups	Particularly patients that use tacrolimus and require medications or herbal remedies which are strong CYP3A4 inhibitors (e.g., such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers (e.g., such as rifampicin, rifabutin) are at risk. Genetic CYP3A polymorphisms may have an impact on drug metabolism and a person's ability to metabolize certain drugs can be increased ("fast" metabolizers) or decreased ("poor" metabolizers). To date, the influence of CYP3A polymorphisms on the metabolism of tacrolimus and clinical consequences thereof remains to be further elucidated. It is not clear whether pharmacogenetic profiling can be a useful clinical tool for identifying high risk patients and better guiding tacrolimus dosing in clinical practice [Chen & Prasad, 2018; Birdwell et al, 2015].
Risk minimization measures	• Routine risk minimization measures: • SmPC Section 4.2 in which a recommendation is given about monitoring of blood trough levels of tacrolimus following co-administration of substances which may alter tacrolimus whole blood concentrations. • SmPC Section 4.4 in which a recommendation is given to closely monitor tacrolimus blood levels, and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure, when used concomitantly with inhibitors or inducers of CYP3A4. • SmPC Sections 4.4 in which a recommendation is given to

Important Identified risk: Interaction with other medication and herbal drugs	
	avoid concomitant use with herbal preparations. • SmPC Sections 4.4 and 4.5 in which a recommendation is given to avoid concomitant use with ciclosporin or potassium-sparing diuretics. • SmPC Sections 4.4 and 4.5 in which a warning is included that certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects.
Risk minimization measures	• SmPC Section 4.5 in which a recommendation is given 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. • SmPC Section 4.5 in which a recommendation is given about other (not related to CYP3A4) interactions potentially leading to increased tacrolimus blood levels. • SmPC Section 4.5 in which a recommendation is given about the effect of tacrolimus on the metabolism of other medicinal products because tacrolimus is a known CYP3A4 inhibitor. • SmPC Section 4.5 in which a recommendation is given about the need of therapeutic drug monitoring of mycophenolic acid (MPA) when switching combination therapy from ciclosporin/MPA to tacrolimus/MPA or vice versa because ciclosporin interferes with the enterohepatic recirculation of MPA. • SmPC Sections 4.4 and 4.5 in which a recommendation is given to avoid the use of live attenuated vaccines. • PL Section 2 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

CYP3A4: Cytochrome P-450 3A4; ECG: Electrocardiogram; MPA: Mycophenolic Acid; PL: Package Leaflet; SmPC: Summary of Product Characteristics

Important Identified risk: Ventricular hypertrophy	
Evidence for linking the risk to the medicine	This important identified risk is based on data from tacrolimus clinical and post-marketing experience.
Risk factors and risk groups	Risk factors include pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema.
Risk minimization measures	Routine risk minimization measures:

Important Identified risk: Ventricular hypertrophy	
	• SmPC Section 4.4 in which recommendations are given to monitor high-risk patients, and if abnormalities develop, to consider dose reduction of tacrolimus therapy, or change of treatment to another immunosuppressive agent. • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

PL: Package Leaflet; SmPC: Summary of Product Characteristics

Important Identified risk: Cardiomyopathies	
Evidence for linking the risk to the medicine	This important identified risk is based on data from tacrolimus clinical and post-marketing experience.
Risk factors and risk groups	Risk factors include pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 in which recommendations are given to monitor high-risk patients, and if abnormalities develop, to consider dose reduction of tacrolimus therapy, or change of treatment to another immunosuppressive agent. • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

PL: Package Leaflet; SmPC: Summary of Product Characteristics

Important Identified risk: Use during pregnancy	
Evidence for linking the risk to the medicine	This important identified risk is based on data from tacrolimus post-marketing experience and on data from the Transplant Pregnancy Registry. This voluntary pregnancy registry was established in 1991 to study the outcomes of pregnancies in SOT recipients in North America and was expanded in 2016, allowing international participation (Transplant Pregnancy Registry International [TPRI]).
Risk factors and risk groups	Not applicable.
Risk minimization measures	Routine risk minimization measures:

Important Identified risk: Use during pregnancy	
	• SmPC Section 4.6, in which recommendation is given to monitor the newborn for the potential adverse effects of tacrolimus in case of in utero exposure. • SmPC Section 4.6, in which recommendation is given that 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 fetus. • PL Section 2 Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Feasibility assessment – Feasibility assessment of conducting a non-interventional post-authorization safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study See [Section II.C] of this summary for an overview of the post-authorization development plan.

NI-PASS: Non-interventional Post Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics; SOT: Solid Organ Transplant; TPRI: Transplant Pregnancy Registry International.

Important Identified risk: Use during lactation	
Evidence for linking the risk to the medicine	This important identified risk is based on data from tacrolimus post-marketing experience and on data from the Transplant Pregnancy Registry. This voluntary pregnancy registry was established in 1991 to study the outcomes of pregnancies in SOT recipients in North America and was expanded in 2016 allowing international participation (Transplant Pregnancy Registry International [TPRI]).
Risk factors and risk groups	Not applicable.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6, in which recommendation is given that women should not breast-feed whilst receiving tacrolimus. • PL Section 2 Additional risk minimization measures • None

Important Identified risk: Use during lactation	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Feasibility assessment – Feasibility assessment of conducting a non-interventional post-authorisation safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study See [Section II.C] of this summary for an overview of the post-authorization development plan.

NI-PASS: Non-interventional Post Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics; SOT: Solid Organ Transplant; TPRI: Transplant Pregnancy Registry International.

II.C Post authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies that are conditions of the marketing authorization or specific obligation of Prograf, Advagraf, and Modigraf.

II.C.2 Other studies in post authorization development plan

Feasibility assessment of conducting a non-interventional post- authorization safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study

Purpose of the assessment:

This will be a non-interventional multi-country feasibility assessment using longitudinal secondary data from large data sources in Finland, Norway, Sweden, the United Kingdom (UK), Denmark and France to assess exposure to tacrolimus and alternative immunosuppressants before conception and during pregnancy among transplant recipients, considering both maternal and paternal exposure. With pregnancy as the unit of analysis, the results will be counts of pregnancies with maternal and paternal exposure to tacrolimus and alternative immunosuppressants, considering the inclusion and exclusion criteria. The index date for each pregnancy will be defined as the date of conception and will determine the start of the observation period for each individual report of pregnancy.