VI.3 Elements for a Public Summary

VI.3.1 Overview of disease epidemiology

Significant numbers of organ transplantation are carried out worldwide every year. Kidney transplantation represent around 70% of all these organs transplantation, followed by liver transplantation (20%), heart transplantation (5%), lung transplantation (<3%) and pancreas transplantation (<3%).

The number of organ transplantation carried out in the European Union varies quite significantly from country to country.

In the EU, approximately 13.9 organ transplantation procedures are performed per million population (pmp) per year. Around 3.5% of these organs are from living donors. In the USA around 20.3 organ transplantation procedures are performed pmp per year.

Among the adults, over 50% of the organ transplantation procedures were performed in patients aged 45 to 64 years of age, with a tendency towards more males requiring organ transplantation thank females (66.7% vs 33.3%). There was no difference in the proportion of male to female organ transplantation in children however, children organ transplantation are generally low (the proportion is lower for kidney and liver transplantation ≤4% than for liver or heart transplantation (around 20%).

Acute rejection of organ transplant occurs in less than 20% of recipients within the first year of transplantation.

The overall survival rates of a recipient of organ transplantation, varied according to the transplanted organ and the source of the organ donor. Around 8 % of adult recipients of a kidney transplant will die or experience organ rejection within one year, in situation where the donor was a deceased donor. Around 3% of the recipients will die or have organ rejection if the donated organ was from a living donor (Department of Health and Human Services Health Resources and Services Administration Healthcare Systems Bureau Division of Transplantation, 2012).

VI.3.2 Summary of treatment benefits

Prograf®, Advagraf® and Modigraf® contain the active substance tacrolimus. It is an immunosuppressant (agent that prevents your body fighting or rejecting foreign substance). Following organ transplantation (liver or kidney), the receipient's immune system percieves the transplanted organ as foreign and tries to reject the new organ. Prograf®, Advagraf® and Modigraf® are used to control the body's immune response, enabling ones body to accept the transplanted organ.

Prograf®, Advagraf® and Modigraf® may also be given for ongoing rejection in already transplanted liver, kidney, heart or other organ when any previous treatment taken was unable to control the immune system response after transplantation. Advagraf® is indicated for used in adults. Prograf® and Modigraf® may also be used in children.

The efficacy and safety of Advagraf (the prolonged released, once daily capsule of tacrolimus) and Prograf (the immediate released twice daily capsules of tacrolimus), both in combinations with corticosteroids, was compared in 471 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%] (indicating no significant difference).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 transplanted organ (graft) survival was 85.3% for Advagraf and 85.6% for Prograf (this is comparable for both drugs).

The efficacy and safety of Advagraf and Prograf Capsules, both in combinations with mycophenolate mofetil (MMF) and corticosteroids, was compared in 667 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%] (indicating no significant difference). The 12-month patient survival rates were 96.9% for Advagraf and 97.5% for Prograf (indicating no significant difference); 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 Capsules, ciclosporin and Advagraf, all in combination with basiliximab antibody induction, MMF and corticosteroids, was compared in 638 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) for Advagraf vs. ciclosporin and -1.9% (Prograf-ciclosporin), 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

These clinical studies have shown that Advagraf can be used safely and is efficacious with recommended regimen for primary immunosupression in adult liver and kidney transplant prophylaxis and for the treatment of rejection resistant to other conventional immunosuppressive regimens in adult transplant recipients.

Conversion of Prograf Capsules-treated patients to Advagraf

Patients that received organ transplant from another person that are 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. When converting from Prograf capsules to Advagraf, the required optimal blood level should be measured prior to conversion and within two weeks after conversion. Following conversion, tacrolimus optimal blood 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.

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 prevention of transplant rejection.

VI.3.3 Unknowns relating to treatment benefits

In 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

Since the ways tacrolimus is absorption, broken down, distributed and excreted from the body are unaffected by renal function (see section 5.2 of SmPC), 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).

Elderly patients

There is no evidence currently available to indicate that dosing should be adjusted in elderly patients.

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.

VI.3.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Torsade de Pointes (irregular heartbeat)	Tacrolimus may uncommonly cause irregular heart beat (prolong the QT interval and may cause Torsade de Pointes).	By using the warning and precaution information in the product label, expressing caution in the use in patients with risk factors for irregular heart beat. These include patients with a personal or family history of QT prolongation, congestive heart failure, irregular heart beat and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to cause irregular heart beat, induce electrolyte abnormalities or known to increase tacrolimus exposure.
Gastrointestinal Perforation	The actual number of GI perforation events in the general population is unknown. However, the incidence rate of GI perforation in the subjects treated with tacrolimus (FK506) under clinical study for liver transplant was 7.8%. GI perforation is a very serious event that needs prompt treatment including surgery.	By using the product label; GI perforation is already listed in the SmPC as an ADR, in light of the seriousness of the event and the requirement for prompt treatment to prevent development of a life-threatening situation, it was considered appropriate to include a warning in section 4.4 of the SmPC as well inclusion in the PIL.
Pure Red Cell Aplasia (a very severe reduction in red blood cell counts)	Pure red cell aplasia (PRCA) describes a condition in which red blood cell precursors in bone marrow are nearly absent while the white blood cell precursors are at normal levels.	Special warning and precaution information is provided in the product label.

Risk	What is known	Preventability
	Congenital PRCA is a lifelong disorder, and is associated with physical abnormalities occurring in 50% of affected children. Acquired or secondary aplasia (PRCA) may be due to the immunosuppressive effect of tacrolimus leading to susceptibility to viral infection that are well known to be a cause of bone marrow suppression (e.g. parvovirus B19, EBV, hepatitis and erythrovirus infection).	
Medication error	There is a potential for Advagraf-Prograf medication error. Following marketing authorization approval in EU, Advagraf-Prograf medication errors have been reported. This resulted in the MAH to conduct a detailed root cause analysis and implementation of risk minimization activities since 2008.	Warning and precaution information about medication errors is provided in the product label. **Additional risk minimization measures have also been done, including**: Direct communication of Advagraf/Prograf medication errors to HCPs across the EEA. Modification of the product labeling packages for Advagraf. Implementation of enhanced routine Pharmacovigilance activities through the use of medication-errors targeted follow-up questionnaires, regular update via periodic reporting to the health authorities and survey (in 2009) to assess the effectiveness of the implemented risk minimization measures. Evidence since implementation, suggests a

Risk	What is known	Preventability
		downwards trending in the reporting of Advagraf – Prograf medication errors.
Blood Cell Changes	Anaemia is commonly observed in renal transplant patients, with a prevalence ranging from 22% to 45%, depending on the definition of anaemia use.	Warning about blood cell changes are in the product label and patient information leaflet.
Cardiac arrhythmias (iregular heart beat)	Ventricular arrhythmias (VAs), including ventricular tachycardia (VT) and ventricular fibrillation (VF), are life-threatening complications of acute myocardial infarction (MI). Uncommon side effects of tacrolimus includes irregular heart beat.	Information about these irregular heart beats including ventricular arrhythmias and supraventricular arrhythmias are provided in the product label and patient information leaflet
Cardiomyopathies (disorder of the heart muscle)	Cardiomyopathies are heart muscle disorders. Cardiomyopathies have been observed in tacrolimus-treated patients on rare occasions.	Warning is provided in the product label and in the patient information leaflet.
Coagulopathies (blood clotting disorders)	The liver plays a central role in the maintenance of haemostasis as the site of synthesis for the vast majority of proteins required for regulation of coagulation and fibrinolysis. Thus, impairment of liver cell function can disturb haemostasis. Blood clot in a vein of a limb and changes in blood clotting are uncommon side effects of tacrolimus.	Warning is provided in the product label and in the patient information leaflet.
Diabetogenicity (Increased blood sugar/Diabetes)	New-onset diabetes and impaired glucose tolerance (IGT) are among the most serious metabolic complications of solid organ	In formation and warning about diabetes provided in the product label and patient information leaflet.

Risk	What is known	Preventability
	transplantation. Despite the importance of these conditions to the outcome of transplant recipients, their precise incidence is difficult to determine. New-onset diabetes is a side effect of tacrolimus.	
Diarrhoea	Diarrhea is a commonly occurring adverse event in post transplant patients with the prevalence reported as high as 72 % [Nepal et al, 2013]. Diarrhoea is a side effect of tacrolimus.	Warning information about significant blood level changes of systemic tacrolimus in recipients with diarrhea is provided in the product label and diarrhea is listed as side effect of Advagraf in the patient information leaflet.
Electrolyte Changes (changes in blood salts levels; including magnesium, phosphate potassium, calcium or sodium)	Renal transplantation can restore glomerular filtration rate (GFR). However other renal functions may not be fully restored such as renal acid-base handling, which may present as electrolyte changes. Changes in blood salts level may also be a side effects of tacrolimus use.	Information about changes in the blood salt and the monitoring of these changes are in the product label and patient information leaflet.
Galactose Intolerance	Galactosemia is a hereditary disorder of galactose metabolism, caused by a deficiency of the enzyme galactose-1 phosphate uridyltransferase. Tacrolimus capsule contain lactose, hence patients with this hereditary disorder are cautioned about the use of this product.	Warning and precaution information is provided in the product label.
Hepatic and Renal Dysfunction (Abnornal Kidney and liver function)	It has been reported that up to 25% of patients will have some degree of abnormal liver functions during the immediate post-transplant period.	There are warnings and precaution in the product label and the patient information leaflet.

Risk	What is known	Preventability
	Abnormality of the liver function, insufficient functioning of the kidneys, reduced production of urine and impaired or painful urination are among the side effects of tacrolimus.	
Hypertension (increased blood pressure)	The incidence of high blood pressure was 52.7% after liver transplantation. Hypertension is also common following renal transplantation, affecting up to 80% of renal transplant patients. Increased blood pressure is a side effect of tacrolimus.	There are warnings and precaution in the product label and the patient information leaflet and insert.
Lactation (exposure through breast milk)	Human data demonstrated that tacrolimus is excreted in breast milk and detrimental effects on the newborn cannot be excluded.	Information and warning on tacrolimus exposure through pregnancy and lactation is discussed in the product label and patient information leaflet.
Neoplasm (benign and malignant turmors)	Benign and malignant tumours have been reported following use of tacrolimus.	Information on benign and malignant turmors are in the patient information leaflet and product label for for Advagraf.
Neurological and Visual disorders	After organ transplantation, some patients suffer mild neurological symptoms, such as tremor, to severe complications, including seizures and encephalopathy. Fits, disturbance of consciousness, blurred vision, increased sensitivity to light and eye disorders are side effects of tacrolimus.	Information and warning on the requirements to monitor neurological and visual status post-transplantation is in the product label and the patient information leaflet.
Pregnancy (exposure in pregnancy)	Human data show that tacrolimus crosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse	Information and warning on tacrolimus exposure through pregnancy is discussed in the product label and patient information leaflet.

Risk	What is known	Preventability
	event or the outcome of the pregnancy. However there have been reported cases of spontaneous abortion.	
Prolonged QT Interval (irregular heartbeat)	Most patients with end-stage liver disease who undergo OLT have a prolonged QT before transplantation, indicating some elements of autonomic dysfunction. Also concomitant use of drugs that may prolong QT interval post organ transplantation may predispose patients on tacrolimus to QT prolongation. Side effects of tacrolimus include irregular heartbeat and abnormal ECG findings.	There is warning in the product label and the patient information leaflet about about irregular heartbeat abnormality of ECG.
Serious Infection and reactivation of pre-existing infections	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.	Information and warnings are in product label and patient information leaflet about Patients treated with immunosuppressant, including Advagraf are at increased risk for opportunistic infections. Infections that have been experienced after use of Advagraf (tacrolimus) are also listed in the product label and patient information document.
Ventricular Hypertrophy (enlargement of the heart muscle)	Ventricular hypertrophy or hypertrophy of the septum, (enlargement of the heart muscle), have been observed in tacrolimus-treated patients on rare occasions. Most cases have been reversible, occurring with tacrolimus blood trough concentrations much higher than the	Warning of the occurrence of enlargement of the heart muscle is in the product label and the patient information leaflet.

Risk	What is known	Preventability
	recommended maximum levels.	

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Interaction with MMF	In a multiple clinical trials there have been incidental reports of adverse events due to potential interaction between systemic tacrolimus and MMF. In a 2-year, open-label, randomized, multicenter trial consisting of 720 renal TX patients (Opticept Trial) in the US, patients received either (A) concentration-controlled MMF (MMF_{CC}) and reduced-level calcineurin inhibitor (MMF_{CC}/CNI_{RL}); (B) MMF_{CC} and standard-level CNI (MMF_{CC}/CNI_{SL}); or (C) fixed-dose MMF and CNI_{SL} (MMF_{FD}/CNI_{SL}). Administered CSIs were either TAC or CsA. TAC was administered to 198, 188 and 196 patients in Groups A, B and C, respectively. Diarrhea was the most commonly observed adverse event in all 3 groups, occurring in almost 50% of TAC-administered patients. Among all 3 groups combined, other common adverse events reported in post-transplantation included leukopenia (27%), hypertension (22%), hyperlipidemia (76%), opportunistic infections (11%), diabetes mellitus (13%) and malignancies (3%). Patients administered TAC with MMF were significantly more likely to experience diarrhea and malignancies when compared to CsA [Gaston et al, 2009]. TAC/MMF, mortality at 12-months was 8% and graft failure was 2%. There were no significant difference in mortality and graft failure in the 2 treatment groups [Ciancio et al, 2004].
Preventability	There are warnings and precautions in the tacrolimus product label section 4.4 and 4.5. These include warning that administration of tacrolimus and other immunosuppressant should be avoided and care taken when administering tacrolimus to patients who have previously received other immunosuppressant drugs. Also the drug-drug interaction section discussed all various potential interactions with tacrolimus.

Risk	What is known (Including reason why it is considered a potential risk)
Medication errors through exchanging tacrolimus capsules and granules.	Clinically relevant difference in bioavailability between the two formulations cannot be excluded. Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, may occur. This could lead to serious adverse reactions, including graft rejection, or other adverse reactions which could be a consequence of either under- or over-exposure to tacrolimus.
Preventability	Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulations or regimen should only take place under the close supervision of a transplant specialist. This is emphasized in Special warning and precaution in section 4.4 of the SmPC and Listed in section 4.8 (undesirable effects). Other routine risk minimisation measures include information in the patient information/insert leaflet to emphasise that tacrolimus is a Prescription Only Medicine (POM) and 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 (SmPC section 4.2).

Important missing information

Not applicable to this version of the RMP

VI.3.5 Summary of additional risk minimisation measures by safety concern

These additional risk minimisation measures are for the following risks:

Medication Error

1. **Direct Healthcare Professional Communication (DHPC**) to specialists, general practitioners, and community and hospital pharmacists (December 2008). Advagraf and Prograf product label were revised to include warning and precaution on the important risk of medication error. Also educating HCPs of the potential risk of unintentional substitution between approved tacrolimus formulations (once-daily extended-release and twice-daily immediate-release versions).
2. **Over-labeling of the Advagraf outer packaging to more clearly differentiate Advagraf from Prograf Capsules (December 2008),**

Medication Error

Risk minimisation measure(s): • Communication plan of Prograf/Advagraf medication errors to HCPs through a DHPC letter in 2008. • Modification (over-labeling) of the product packaging and labeling for Advagraf, including the patients information leaflet (PIL) and outer packaging of the medicinal products in 2008/2009.
Objective and rationale: • To notify and inform patients, and HCPs of the risk of medication error with systemic tacrolimus. • The package and product label changes was to enhance product recognition and decrease confusion between Advagraf (prolong release once daily capsule) and Prograf (immediate release, twice daily capsule).
Following marketing approval of Advagraf in EU, medication errors have been reported including incorrect frequency of dosing (i.e., once daily Advagraf dosing and twice daily Prograf Capsules dosing); inadvertent, unintentional or unsupervised substitution of one formulation for the other; and co-administration of the 2 formulations. Results of a detailed root cause analysis indicate that these errors can be classified at the level of prescribing (by physicians), dispensing (by pharmacist) and administration (by physician, nurse or patient). A proposal for risk minimization measures was submitted along with the notification to the Health Authorities. The main additional risk minimisation measures employed are: • Direct Healthcare Professional Communication (DHPC) to specialists, general practitioners and community and hospital pharmacists (December 2008). Advagraf and Prograf product label were revised to include warning and precaution on the important risk of medication error. Also educating HCPs of the potential risk of unintentional substitution between approved tacrolimus formulations (once-daily extended-release and twice-daily immediate-release versions). • Over-labeling of the Advagraf outer packaging to more clearly differentiate Advagraf from Prograf Capsules (December 2008),

VI.3.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Not applicable for this version of RMP

Studies which are a condition of the marketing authorisation

Not applicable for this version of the RMP.

VI.3.7 Summary of changes to the Risk Management Plan over time

The following changes were in the previous Advagraf and Modigraf RMPs, and have been incorporated into this systemic tacrolimus RMP.

Table 14 Major changes to Previous Risk Management Plans over time

Version	Date	Safety Concerns	Comment
Advagraf Version 4	June 2011	Important potential risk of interaction with MMF	Update to the safety specification of RMP to include the important potential risk of interaction with MMF
Advagraf Version 5	May 2012	Important identified risks: Pure red cell aplasia (PRCA) and medication error	Safety specification of the RMP updated to include important indentified risk of pure red cell aplasia (PRCA)
Advagraf Version 6	August 2013	Important identified risks: Torsade de Pointes and Gastrointestinal perforation (GI perforation)	Update to the RMP safety specification to include the important identified risk of Tdp and GI perforation
Modigraf Version 2.0	12 September 2007	RMP creation/ update in line with regulatory requirements	
Modigraf Version 3.0	16 October 2008	Need for RM activities should be assessed for each safety concern. If safety information is expected from ongoing clinical or non-clinical studies this shuld be listed against the specific safety concern.	Align identified risks in safety specification to those in summary later in document. Add summary of the EU-RMP including all PV and RM activities for each safety concern. RMP should contain no references to other modules.
Modigraf Version 3.1	February 2009	Potential risks of overdosage, underdosage and medication errors with Modigraf granules JC virus and BK virus infections and their associations to progressive	

Version	Date	Safety Concerns	Comment
		multifocal leukoencephalopathy (PML) and nephropathy respectively mentioned in SPC and RMP	
Modigraf Version 3.2	March 2009	Include FUM on paediatric study (what is now OPTION and PROGRESSION)	Align RMP with last SPC and PIL updates
Modigraf Version 4.0	June 2013	Addition of Torsades de Point and GI perforations	Alignment with the Advagraf RMP. Modigraf renewal procedure and update to new template.