PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE:

TEVLIGRAF 0,5 (Prolonged-release hard capsule)

TEVLIGRAF 1 (Prolonged-release hard capsule)

TEVLIGRAF 3 (Prolonged-release hard capsule)

TEVLIGRAF 5 (Prolonged-release hard capsule)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

TEVLIGRAF 0,5: Each prolonged-release hard capsule contains 0,5 mg tacrolimus (as monohydrate).

Excipients with known effect:

Contains lactose monohydrate 53,725 mg per prolonged-release hard capsule.

TEVLIGRAF 1: Each prolonged-release hard capsule contains 1 mg tacrolimus (as monohydrate).

Excipients with known effect:

Contains lactose monohydrate 107,45 mg per prolonged-release hard capsule.

TEVLIGRAF 3: Each prolonged-release hard capsule contains 3 mg tacrolimus (as monohydrate).

Excipients with known effect:

Contains lactose monohydrate 322,35 mg per prolonged-release hard capsule.

TEVLIGRAF 5: Each prolonged-release hard capsule contains 5 mg tacrolimus (as monohydrate).

Excipients with known effect:

Contains lactose monohydrate 537,25 mg per prolonged-release hard capsule.

For the full list of excipients see **section 6.1**.

3. PHARMACEUTICAL FORM:

Prolonged-release hard capsules.

TEVLIGRAF 0,5: Size 5 hard gelatin capsules filled with white to off-white powder. Body: light orange with “0,5 mg” radial black imprinting. Cap: light yellow with “TR” radial black imprinting.

TEVLIGRAF 1: Size 4 hard gelatin capsules filled with white to off-white powder. Body: light orange with “1 mg” radial black imprinting. Cap: White with “TR” radial black imprinting.

TEVLIGRAF 3: Size 1 hard gelatin capsules filled with white to off-white powder. Body: light orange with “3 mg” radial black imprinting. Cap: light orange with “TR” radial black imprinting.

TEVLIGRAF 5: Size 0 hard gelatin capsules filled with white to off-white powder. Body: light orange with “5 mg” radial black imprinting. Cap: greyish red with “TR” radial black imprinting.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

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

Treatment of allograft rejection resistant to treatment with other immunosuppressive medicines in adult patients.

4.2 Posology and method of administration:

Posology:

Inadvertent, unintentional or unsupervised switching between immediate- and prolonged-release formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, 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. Following conversion to any alternative formulation, therapeutic medicine monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

General statement:

The recommended initial dosages presented below are intended to act solely as a guideline. Tacrolimus is routinely administered in conjunction with other immunosuppressive medicines in the initial post-operative transplant period. The tacrolimus dose may vary depending upon the immunosuppressive regimen chosen. Tacrolimus dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring. If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.

Duration of dosing:

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

Dosage recommendations - Prophylaxis of Transplant Rejection: Kidney transplantation:

Initial dose (primary immunosuppression):

Oral TEVLIGRAF therapy should commence at a dose of 0,20 to 0,30 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery.

Maintenance therapy:

TEVLIGRAF doses are usually reduced during maintenance therapy. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to TEVLIGRAF-based

dual therapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate dose adjustment.

Dosage recommendations - Prophylaxis of Transplant Rejection: Liver transplantation:

Initial dose (primary immunosuppression):

Oral TEVLIGRAF therapy should commence at a dose of 0,10 to 0,20 mg/kg/day administered once daily in the morning. Administration should commence approximately 12 to 18 hours after the completion of surgery.

Maintenance therapy:

TEVLIGRAF doses are usually reduced during maintenance therapy. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to TEVLIGRAF monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate dose adjustment.

Dosage recommendations – Conversion of immediate release formulation tacrolimus treated patients to TEVLIGRAF:

Allograft transplant patients maintained on twice daily tacrolimus immediate release formulation dosing requiring conversion to once daily TEVLIGRAF should be converted on a 1:1 (mg/mg) total daily dose basis. TEVLIGRAF should be administered in the morning. Following conversion, tacrolimus trough levels should be monitored and if necessary dose adjustments made to maintain similar systemic exposure.

D**osage recommendations - Rejection therapy:**

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 are noted (e.g. pronounced adverse reactions) the dose of TEVLIGRAF may need to be reduced.

For information on conversion from ciclosporin to TEVLIGRAF, see below under **DOSAGE ADJUSTMENTS IN SPECIAL POPULATIONS.**

Kidney and liver transplantation:

For conversion from other immune-suppressants to once daily TEVLIGRAF, treatment should begin with the initial oral dose recommended for primary immunosuppression.

Heart transplantation:

In adult patients converted to TEVLIGRAF, an initial oral dose of 0,15 mg/kg/day should be administered once daily.

Other allografts transplantation:

No data for TEVLIGRAF for lung-transplanted, pancreas-transplanted and intestine transplanted patients are available.

DOSAGE ADJUSTMENTS IN SPECIAL POPULATIONS:

Liver impairment:

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

Kidney impairment:

No dose adjustment is necessary as the pharmacokinetics of tacrolimus are unaffected by renal function. However, careful monitoring of renal function (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output) is recommended.

Elderly population:

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

Race:

In comparison to Caucasians, non-Caucasian patients may require higher tacrolimus doses to achieve similar trough levels.

Conversion from ciclosporin to TEVLIGRAF:

Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. TEVLIGRAF 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 to 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected.

Therapeutic drug monitoring:

Various assays have been used to measure blood or plasma levels of tacrolimus. Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting medicines and the post-transplant time interval. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies.

Whole blood specimens should be collected into tubes containing ethylene diamine tetra acetic acid (EDTA) anticoagulant. Heparin anticoagulation is not recommended because of

the tendency to form clots on storage. Samples that are not analysed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept longer they should be deep frozen at - 20 ºC for up to 12 months.
Blood trough levels of tacrolimus should be monitored during the post-transplantation period. Blood trough levels for tacrolimus should be drawn approximately 24 hours post-dosing, just prior to the next dose. The frequency of blood level monitoring should be based on clinical needs. As tacrolimus as contained in TEVLIGRAF is a medicinal product with low clearance, adjustments to the TEVLIGRAF dosage regimen may take several days before changes in blood levels are apparent. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be monitored following dose adjustment, changes in the immunosuppressive regimen, or following co-administration of substances which may alter tacrolimus whole blood concentrations. Clinical experience suggests that the majority of patients can be successfully managed if tacrolimus blood levels are maintained below 25 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 of 5 to 20 ng/ml in liver transplant recipients and 10 to 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 to 15 ng/ml in liver, kidney and heart transplant recipients.

Paediatric population:

The safety and efficacy of tacrolimus in children under 18 years has not yet been established. Limited data is available but no recommendation on a dosage can be made.

Method of administration:

It is recommended that the oral daily dose of TEVLIGRAF be administered once daily in the morning. TEVLIGRAF prolonged-release capsules should be taken immediately following removal from the blister. The capsules should be swallowed with fluid (preferably water). TEVLIGRAF 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. If a patient had forgotten to take the morning dose, they should take their dose as soon as possible on the same day. A double dose should not be taken the next morning.

4.3 Contraindications:

- Known hypersensitivity to tacrolimus the active ingredient of TEVLIGRAF or other macrolides or to any of the excipients listed in **section 6.1**.
- Pregnancy and lactation (see **section 4.6**).
- As tacrolimus, the active ingredient of TEVLIGRAF may alter the metabolism of oral contraceptives, other forms of contraception should be used (see **section 4.5**).
- Known hypersensitivity to polyoxyethylated castor oil (HCO-60) or structurally related compounds.
- Concomitant administration of live attenuated vaccines.
- Concomitant administration with ciclosporin.
- Concomitant use with grapefruit juice.

4.4 Special warnings and precautions for use:

Prolonged-release formulations of tacrolimus such as TEVLIGRAF are not interchangeable with immediate-release formulations of tacrolimus, without careful monitoring and supervision by a transplant specialist.

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations such as TEVLIGRAF, 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 **section 4.2** and **4.8**).
TEVLIGRAF 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 medicines in adult patient's clinical data are not yet available for the prolonged-release formulation of tacrolimus, TEVLIGRAF.

For prophylaxis of transplant rejection in adult heart allograft recipients, clinical data are not yet available for tacrolimus formulations such as TEVLIGRAF.

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 TEVLIGRAF after consulting a transplant specialist, due to the potential for drug interactions resulting in serious adverse reactions including rejection or toxicity (see **section 4.5**).

CYP3A4 inhibitors:

Concomitant use with CYP3A4 inhibitors may increase tacrolimus blood levels, which could lead to serious adverse reactions, including nephrotoxicity, neurotoxicity and QT-prolongation. It is recommended that concomitant use of strong CYP3A4 inhibitors (such as ritonavir, cobicistat, ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin or josamycin) with TEVLIGRAF should be avoided. If unavoidable, tacrolimus blood levels should be monitored frequently, starting within the first few days of co-administration, under the supervision of a transplant specialist, to adjust the TEVLIGRAF dose if appropriate in order to maintain similar tacrolimus exposure.

Renal function, ECG including the QT-interval, and the clinical condition of the patient should also be closely monitored.

Dose adjustment needs to be based upon the individual situation of each patient. An immediate dose reduction at the time of treatment initiation may be required (see **section 4.5**).

Similarly, discontinuation of CYP3A4 inhibitors may affect the rate of metabolism of tacrolimus, thereby leading to sub-therapeutic blood levels of tacrolimus, and therefore requires close monitoring and supervision of a transplant specialist.

CYP3A4 inducers:

Concomitant use with CYP3A4 inducers may decrease tacrolimus blood levels, potentially increasing the risk of transplant rejection. It is recommended that concomitant use of strong CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine) with TEVLIGRAF should be avoided. If unavoidable, tacrolimus blood levels should be monitored frequently, starting within the first few days of co-administration, under the supervision of a transplant specialist, to adjust the TEVLIGRAF dose if appropriate, in order to maintain similar tacrolimus exposure. Graft function should also be closely monitored (see **section 4.5**).

Similarly, discontinuation of CYP3A4 inducers may affect the rate of metabolism of tacrolimus, thereby leading to supra-therapeutic blood levels of tacrolimus, and therefore requires close monitoring and supervision of a transplant specialist

P-glycoprotein:

Caution should be observed when co-administering TEVLIGRAF with medicines 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 TEVLIGRAF dose may be required (see **section 4.5**).

Herbal preparations:

Herbal preparations containing St. John's wort (*Hypericum perforatum*) or other herbal preparations should be avoided when taking tacrolimus containing products such as TEVLIGRAF due to the risk of interactions that lead to either a decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus or an increase of blood concentrations of tacrolimus and risk of tacrolimus toxicity (see **section 4.5**).

Other interactions:

TEVLIGRAF should not be administered together with ciclosporin (see **section 4.5**).
High potassium intake or potassium-sparing diuretics should be avoided (see **section 4.5**).
Certain combinations of TEVLIGRAF with medicines known to have neurotoxic effects may increase the risk of these effects (see **section 4.5**).

Vaccination:

Immuno-suppressants may affect the response to vaccination and vaccination during treatment with TEVLIGRAF may be less effective. The use of live attenuated vaccines should be avoided.

Nephrotoxicity:

Tacrolimus such as TEVLIGRAF 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 TEVLIGRAF is concomitantly administered with medicines associated with nephrotoxicity (see **section 4.5**). Concurrent use of TEVLIGRAF with medicines 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 such as TEVLIGRAF. 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.

Monitoring of blood concentrations of tacrolimus is recommended during episodes of diarrhoea as concentrations may be significantly affected.

Cardiac disorders:

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, has been observed, with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. High-risk patients, particularly young children and those receiving substantial immunosuppression should be monitored accordingly, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at three months and then at 9 to 12 months). If abnormalities develop, dose

reduction of TEVLIGRAF therapy, or change of treatment to another immunosuppressive medicine should be considered. Tacrolimus as contained in TEVLIGRAF may prolong the QT-interval and may cause *Torsades de Pointes*. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT-Syndrome or acquired QT-prolongation or patients on concomitant medications known to prolong the QT-interval, induce electrolyte abnormalities or known to increase tacrolimus exposure (see **section 4.5**).

Lymphoproliferative disorders and malignancies:

Patients treated with tacrolimus such as TEVLIGRAF have been reported to develop Epstein-Barr virus (EBV)-associated lymphoproliferative disorders (see **section 4.8**). Patients switched to TEVLIGRAF therapy should not receive anti-lymphocyte treatment concomitantly. 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.

Exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

The risk of secondary cancer is unknown (see **section 4.8**).

Infections including opportunistic infections:

Patients treated with immunosuppressants, including TEVLIGRAF, are at increased risk for infections including opportunistic infections (bacterial, fungal, viral and protozoal) such as CMV infection, BK virus-associated nephropathy and John Cunningham (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 can lead to serious or fatal conditions including graft rejection that medical practitioners 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):

Reports of posterior reversible encephalopathy syndrome (PRES) have been received in patients treated with tacrolimus. If patients taking TEVLIGRAF 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 control and immediate discontinuation of TEVLIGRAF is advised. Most patients completely recover after appropriate measures are taken.

Eye disorders:

Eye disorders, sometimes progressing to loss of vision, have been reported in patients treated with tacrolimus as contained in TEVLIGRAF. Some cases have reported resolution on switching to alternative immunosuppression. Patients should be advised to report changes in visual acuity, changes in colour vision, blurred vision, or visual field defect, and in such cases, prompt evaluation is recommended with referral to an ophthalmologist as appropriate.

Pure Red Cell Aplasia:

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus as contained in TEVLIGRAF. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA.

Special populations:

There is limited experience in non-Caucasian patients and patients at elevated immunological risk (e.g. re-transplantation, evidence of panel reactive antibodies, PRA).

Dose reduction may be necessary in patients with severe liver impairment (see **section 4.2**).

Excipients:

Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ponceau 4R: This may cause allergic reactions.

4.5 Interaction with other medicines 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 medicines or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease TEVLIGRAF blood levels. Similarly, discontinuation of such medicines or herbal remedies may affect the rate of metabolism of tacrolimus and thereby the blood levels of tacrolimus.

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels:

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 TEVLIGRAF dose if appropriate in order to maintain similar tacrolimus exposure (see **sections 4.2** and **4.4**). Similarly, patients should be closely monitored when using

TEVLIGRAF concomitantly with multiple substances that affect CYP3A4 as the effects on tacrolimus exposure may be enhanced or counteracted.

Medicines which have effects on tacrolimus, as contained in TEVLIGRAF, 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 medicine that is co-administered with TEVLIGRAF 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.

Medicines which have effects on tacrolimus:

Medicines/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) (see **section 4.4**).	Avoid grapefruit or grapefruit juice.
Ciclosporin	May increase tacrolimus whole blood trough concentrations. In addition, synergistic/additive	The simultaneous use of ciclosporin and tacrolimus should be avoided (see **section 4.4**).

	nephrotoxic effects can occur	
Products known to have nephrotoxic or neurotoxic effects: aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole + trimethoprim, NSAIDs, ganciclovir, acyclovir, amphotericin B, ibuprofen, cidofovir, foscarnet	May enhance nephrotoxic or neurotoxic effects of tacrolimus.	Concurrent use of tacrolimus with medicines known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided, monitor renal function and other side effects and adjust tacrolimus dose if needed.
Strong CYP3A4 inhibitors: antifungal medicines (e.g., ketoconazole, itraconazole, posaconazole, voriconazole), the macrolide antibiotics (e.g., telithromycin, troleandomycin, clarithromycin, josamycin), HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g. telaprevir, boceprevir, and the combination of ombitasvir	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 (see section 4.4). Rapid and sharp increases in tacrolimus levels may occur, as early as within 1 to 3 days after co-administration, despite immediate reduction of	It is recommended that Concomitant use should be avoided. If co-administration of a strong CYP3A4 inhibitor is unavoidable, consider omitting the dose of tacrolimus the day the strong CYP3A4 inhibitor is initiated. Reinitiate tacrolimus the next day at a reduced dose based on tacrolimus blood concentrations. Changes in both tacrolimus dose and/or dosing frequency should be

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.	tacrolimus dose. Overall tacrolimus exposure may increase > 5 fold. When ritonavir combinations are co-administered, tacrolimus exposure may increase > 50 fold. Nearly all patients may require a reduction in tacrolimus dose and temporary interruption of tacrolimus may also be necessary. The effect on tacrolimus blood concentrations may remain for several days after co-administration is completed.	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.
Moderate or weak CYP3A4 inhibitors: antifungal medicines (e.g., fluconazole, isavuconazole, clotrimazole, miconazole), the macrolide antibiotics (e.g., azithromycin), calcium channel blockers (e.g.,	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT-prolongation) (see **section**	Monitor tacrolimus whole blood trough concentrations frequently, starting within the first few days of co-administration. Reduce tacrolimus dose if needed (see **section 4.2**). Monitor renal function, ECG for QT-

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 *Schisandra sphenanthera.*	**4.4**). A rapid increase in tacrolimus level may occur.	prolongation, and other side effects closely.
In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen.	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT-prolongation) (see **section 4.4**).	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed (see **section 4.2**). Monitor renal function, ECG for QT-prolongation, and other side effects closely.

Strong CYP3A4 inducers: rifampicin, phenytoin carbamazepine, apalutamide, enzalutamide, mitotane, or St. John's wort *(Hypericum perforatum)*.	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection (see **section 4.4**). Maximal effect on tacrolimus blood concentrations may be achieved 1 to 2 weeks after co-administration. The effect may remain 1 to 2 weeks after completion of the treatment	It is recommended that concomitant use should be avoided. If unavoidable, patients may require an increase in tacrolimus dose. Changes in tacrolimus dose should be individualized and adjusted as needed based on tacrolimus trough concentrations, which should be assessed at initiation, monitored frequently throughout (starting within the first few days) and re-evaluated on and after completion of the CYP3A4 inducer. After use of the CYP3A4 inducer has ended, tacrolimus dose may need to be adjusted gradually. Monitor graft function closely.
Moderate CYP3A4 inducers: metamizole, phenobarbital, isoniazid, rifabutin, efavirenz, etravirine,	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection (see **section 4.4**).	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed (see **section**

nevirapine; weak CYP3A4 inducers: flucloxacillin.		**4.2**). 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 4.2** and **4.4**).
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 4.2**).
Prokinetic medicines: 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 4.2**). 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 4.4**)	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed (see **section 4.2**). 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.

As TEVLIGRAF treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g. amiloride, triamterene, or spironolactone) should be avoided (see **section 4.4**). Care should

be taken when TEVLIGRAF is co-administered with other medicines 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 medicines:

Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of TEVLIGRAF with medicines known to be metabolised by CYP3A4 may affect the metabolism of such medicines.

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 TEVLIGRAF is not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see **sections 4.2** and **4.4**).

Tacrolimus such as TEVLIGRAF 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. Medicines which interfere with mycophenolic acid's enterohepatic cycle have

potential to reduce the plasma level and efficacy of mycophenolic acid. Therapeutic drug monitoring of mycophenolic acid may be appropriate when switching from ciclosporin to tacrolimus or vice versa.

Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided (see **section 4.4**).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

TEVLIGRAF is contraindicated in pregnancy (see **section 4.3**). Tacrolimus such as TEVLIGRAF has been shown to be teratogenic at doses that also demonstrated maternal toxicity. Preclinical and human data show that tacrolimus is able to cross the placenta.
The possibility of pregnancy should be excluded before initiating TEVLIGRAF therapy.

Breastfeeding:

Human data demonstrate that tacrolimus such as TEVLIGRAF is excreted in breast milk. As detrimental effects on the new born cannot be excluded, women should not breastfeed whilst receiving TEVLIGRAF.

Fertility:

A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats, see **section 5.3**.
No human data is available.

4.7 Effects on ability to drive and use machines:

Tacrolimus such as TEVLIGRAF may cause visual and neurological disturbances. Patients treated with TEVLIGRAF who are affected by such disorders should not drive a car or

operate dangerous machines. This effect may be enhanced if TEVLIGRAF is administered in association with alcohol.

4.8 Undesirable effects:

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

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

Infections and infestations:

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 John Cunningham (JC) virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including tacrolimus.

Neoplasms benign, malignant and unspecified:

Patients receiving immunosuppressive therapy such as TEVLIGRAF are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment such as TEVLIGRAF.

List of adverse reactions:

Infections and infestations:

Frequent: Viral, bacterial, fungal, protozoal infections.

Frequency unknown: BK virus associated nephropathy, John Cunningham (JC) virus associated progressive multifocal leukoencephalopathy (PML).

Neoplasms benign, malignant and unspecified:

Frequency unknown: Epstein-Barr Virus (EBV) -associated lymphoproliferative disorders skin malignancies.

Blood and lymphatic system disorders:

Frequent: Anaemia, thrombocytopenia, leukopenia, red blood cell analyses abnormal, leucocytosis.

Less frequent: Coagulopathies, pancytopenia, neutropenia, coagulation and bleeding analyses abnormal, thrombotic thrombocytopenic purpura, hypoprothrombinaemia, thrombotic microangiopathy.

Frequency unknown: Pure red cell aplasia, agranulocytosis, haemolytic anaemia, febrile neutropenia.

Immune system disorders:

Frequency unknown: Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see **section 4.4**).

Endocrine disorders:

Less frequent: Hirsutism.

Metabolism and nutrition disorders:

Frequent: Diabetes mellitus, hyperglycaemic conditions, hyperkalaemia, metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridemia, hypophosphatemia.

Less frequent: Dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphatemia.

Psychiatric disorders:

Frequent: Insomnia, confusion and disorientation, depression, anxiety symptoms, hallucination, mental disorders, depressed mood, mood disorders and disturbances, nightmare.

Less frequent: Psychotic disorder.

Nervous system disorders:

Frequent: Headache, tremor, nervous system disorders seizures, disturbances in consciousness, peripheral neuropathies, dizziness, paraesthesia's and dysesthesia, impaired writing.

Less frequent: Encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, speech and language abnormalities, paralysis and paresis, amnesia, hypertonia, myasthenia.

Frequency unknown: Posterior reversible encephalopathy syndrome (PRES).

Eye disorders:

Frequent: Blurred vision, photophobia, and eye disorders.

Less frequent: Cataract, blindness.

Frequency unknown: Optic neuropathy.

Ear and labyrinth disorders:

Frequent: Tinnitus.

Less frequent: Hypoacusis, neurosensory deafness, impaired hearing.

Cardiac disorders:

Frequent: Ischaemic coronary artery disorders, tachycardia.

Less frequent: Heart failures, ventricular dysrhythmias and cardiac arrest, supraventricular dysrhythmias, cardiomyopathies, ventricular hypertrophy, palpitations, pericardial effusion, *Torsades de Pointes*.

Vascular disorders:

Frequent: Hypertension, thromboembolic and ischaemic events, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders.

Less frequent: Deep limb venous thrombosis, shock, infarction.

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammation.

Less frequent: Respiratory failure, respiratory tract disorders, asthma, acute respiratory distress syndrome.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, 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.

Less frequent: Acute and chronic pancreatitis, paralytic ileus, gastro-oesophageal reflux disease, impaired gastric emptying, pancreatic pseudocyst, subileus.

Hepato-biliary disorders:

Frequent: Bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice.

Less frequent: Veno-occlusive liver disease, hepatitic artery thrombosis, hepatic failure.

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus, alopecia, acne, increased sweating.

Less frequent: Dermatitis, photosensitivity, toxic epidermal necrolysis (Lyell's syndrome), Stevens Johnson syndrome.

Musculoskeletal and connective tissue disorders:

Frequent: Arthralgia, back pain, muscle spasms, pain in extremity.

Less frequent: Joint disorders, mobility decreased.

Renal and urinary disorders:

Frequent: Renal impairment, acute renal failure, renal failure, toxic nephropathy, renal tubular necrosis, urinary abnormalities, oliguria, bladder and urethral symptoms.

Less frequent: Haemolytic uraemic syndrome, anuria, nephropathy, haemorrhagic cystitis.

Reproductive system and breast disorders:

Less frequent: Dysmenorrhoea, uterine bleeding.

General disorders and administration site conditions:

Frequent: Asthenic conditions, febrile disorders, oedema, pain and discomfort, disturbed body temperature perception.

Less frequent: Influenza like illness, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance, fall, ulcer, chest tightness, thirst, fat tissue increased

Investigations:

Frequent: Abnormal liver function tests, increased blood alkaline phosphatase, increased weight.

Less frequent: Increased amylase, abnormal ECG investigations, abnormal heart rate and pulse investigations, decreased weight, increased blood lactate dehydrogenase, abnormal echocardiogram, prolonged electrocardiogram QT.

Injury, poisoning and procedural complications:

Frequent: 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 (unknown frequency).

Description of selected adverse reactions:

Pain in extremity has been described in a number of published case reports as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS). This typically presents as a bilateral and symmetrical, severe, ascending pain in the lower extremities and may be associated with supra-therapeutic levels of tacrolimus. The syndrome may respond to tacrolimus dose reduction. In some cases, it was necessary to switch to alternative immunosuppression.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reactions Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose:

Experience of over dosage is limited.

Several cases of accidental overdose have been reported with tacrolimus such as TEVLIGRAF: 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 TEVLIGRAF 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 TEVLIGRAF 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, the use of adsorbents (such as activated charcoal) may be helpful, if used shortly after intake.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A.34 Other (Immuno-suppressive macrolide lactone).

Pharmacotherapeutic group: Immunosuppressants, calcineurin inhibitors, ATC code: L04AD02

Mechanism of action:

Tacrolimus is an immunosuppressive agent with activity in both *in vitro* and *in vivo* experiments. Tacrolimus inhibits the formation of cytotoxic lymphocytes that 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 interleukin-2, -3 and γ-interferon and the expression of the interleukin-2 receptor. On the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP), which is also responsible for the intracellular accumulation of the compound.

5.2 Pharmacokinetic properties:

Absorption:

In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Available tacrolimus is generally rapidly absorbed. Tacrolimus 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 immediate release formulation) is in the range of 20 % to 25 % (individual range in adult patients 6 % to 43 %). The oral bioavailability of tacrolimus such as TEVLIGRAF was reduced when it was administered after a meal. Both the rate and extent of absorption of tacrolimus such as TEVLIGRAF were reduced when administered with food.
Bile flow does not influence the absorption of tacrolimus and therefore treatment with TEVLIGRAF may commence orally.
A strong correlation exists between AUC and whole blood trough levels at steady-state for tacrolimus as contained in TEVLIGRAF. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

Distribution:

The disposition of tacrolimus after intravenous infusion may be described as biphasic.
In the systemic circulation, tacrolimus binds strongly to erythrocytes resulting in an approximate 20:1 distribution ratio of whole blood/plasma concentrations. In plasma, tacrolimus is highly bound (> 98,8 %) to plasma proteins, mainly to serum albumin and α-1-acid glycoprotein.
Tacrolimus is extensively distributed in the body. The steady-state volume of distribution based on plasma concentrations is approximately 1300 l (healthy subjects). Corresponding data based on whole blood averaged 47,6 l.

Biotransformation:

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

Elimination:

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance estimated from whole blood concentrations was 2,25 l/h. In adult liver, kidney and heart transplant patients, values of 4,1 l/h, 6.7 l/h and 3,9 l/h, respectively, have been observed. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of tacrolimus, or corticosteroid-induced increased metabolism, are considered to be responsible for the higher clearance rates observed following transplantation.

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

Following intravenous and oral administration of ^{14}C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2 % of the radioactivity was eliminated in the urine. Less than 1 % of unchanged tacrolimus was detected in the urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

Special populations:

Relationship between plasma/blood concentrations and therapeutic activity:

Individual dose adjustment controlled by monitoring of tacrolimus levels in whole blood may be helpful to achieve optimal therapy.

Several immunoassays are available for determining tacrolimus concentrations in whole blood, including a fully automatic micro particle enzyme immunoassay (MEIA).

Elderly:

Based on preliminary clinical experience, the kinetic properties of tacrolimus are not altered in elderly patients.

Hepatic impairment:

Patients with liver dysfunction tended to have higher tacrolimus concentrations (and correspondingly longer half-lives and smaller clearance values) compared with patients with normal liver function.

As tacrolimus is extensively metabolised by the liver, patients with impaired liver function should be carefully monitored, and dose adjustment may be necessary.

Renal impairment:

Since tacrolimus is nearly completely metabolised, highly lipid-soluble, and has a molecular weight of 822 g/mole, it is not expected to be dialysable. Also, less than 1 % of an administered intravenous dose is excreted in the urine. Therefore, changes to the dosing regimen from the pharmacokinetic point of view are not necessary in patients with renal failure or in patients undergoing dialysis. However, dosage adjustment may be necessary in patients with evidence of medicine-induced impairment of kidney function.

5.3 Preclinical safety data:

The kidneys and the pancreas were the primary organs affected in toxicity studies performed in rats and baboons. In rats, tacrolimus caused toxic effects to the nervous system and the eyes. Reversible cardiotoxic effects were observed in rabbits following intravenous administration of tacrolimus.

When tacrolimus is administered intravenously as rapid infusion/bolus injection at a dose of 0,1 to 1,0 mg/kg, QTc-prolongation has been observed in some animal species. Peak blood concentrations achieved with these doses were above 150 ng/mL, which is more than 6-fold higher than mean peak concentrations observed with tacrolimus in clinical transplantation.
Embryo-foetal toxicity was observed in rats and rabbits and was limited to doses that caused significant toxicity in maternal animals. In rats, female reproductive function including birth was impaired at toxic doses and the offspring showed reduced birth weights, viability and growth.
A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Ethylcellulose (Ethocel Standard 10FP Premium)

Hypromellose, type 2910

Lactose monohydrate

Magnesium stearate

Hard gelatin capsule cap & body:

Black iron oxide (E 172) (only TEVLIGRAF 5)

Gelatin

Ponceau 4R (only TEVLIGRAF 5)

Red iron oxide (E 172),

Titanium dioxide (E 171)

Yellow iron oxide (E 172)

Printing ink:

Black Iron Oxide

Potassium Hydroxide

Propylene Glycol

Shellac

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

TEVLIGRAF 0,5 and 1: 24 months.

TEVLIGRAF 3 and 5: 30 months.

6.4 Special precautions for storage:

Store at or below 25 °C.

Store in the original package to protect from light and moisture.

6.5 Nature and contents of container:

TEVLIGRAF 0,5: Capsules are packed into PVC/PVdC-Aluminium blisters. Blisters are packed into a multilayer aluminium pouch with desiccant.

Packs of 30, 50 and 100 prolonged-release capsules are available.

TEVLIGRAF 1: Capsules are packed into PVC/PVdC-Aluminium blisters. Blisters are packed into a multilayer aluminium pouch with desiccant.

Packs of 30, 50, 60 and 100 prolonged-release capsules are available.

TEVLIGRAF 3: Capsules are packed into PVC/PVdC-Aluminium blisters. Blisters are packed into a multilayer aluminium pouch with desiccant.

Packs of 30, 50 and 100 prolonged-release capsules are available.

TEVLIGRAF 5: Capsules are packed into PVC/PVdC-Aluminium blisters. Blisters are packed into a multilayer aluminium pouch with desiccant.

Packs of 30, 50 and 100 prolonged-release capsules are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

8. REGISTRATION NUMBER(S):

TEVLIGRAF 0,5: 52/34/0220

TEVLIGRAF 1: 52/34/0221

TEVLIGRAF 3: 52/34/0222

TEVLIGRAF 5: 52/34/0223

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

14 December 2021

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10 November 2022