SCHEDULING STATUS:
South Africa: S4
Namibia: NS2
Kenya: POM

PROPRIETARY NAME AND DOSAGE FORM
ADVAGRAF 0,5 mg (Prolonged-release capsules)
ADVAGRAF 1 mg (Prolonged-release capsules)
ADVAGRAF 5 mg (Prolonged-release capsules)

COMPOSITION
ADVAGRAF 0,5 mg (Prolonged-Release Capsules); ADVAGRAF 1 mg (Prolonged-Release Capsules); ADVAGRAF 5 mg (Prolonged-Release Capsules):
Active Ingredient: Each capsule contains 0,5 mg, 1 mg and 5 mg tacrolimus, respectively.
Excipients:
Capsule contents: hypromellose, ethylcellulose, lactose monohydrate, magnesium stearate. Capsule shell: titanium dioxide (E 171), yellow iron oxide (E 172), red iron oxide (E 172), sodium laurilsulfate, gelatin.
Printing ink of capsule shell: shellac, lecithin (soya), simeticone, red iron oxide (E 172), hydroxypropylcellulose.
Contains sugar: lactose

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

PHARMACOLOGICAL ACTION

Pharmacodynamic properties
Tacrolimus has immunosuppressive properties. 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.

Pharmacokinetic properties

General characteristics:
Absorption
In man, tacrolimus has been shown to be absorbed throughout the gastrointestinal tract.
Tacrolimus in ADVAGRAF is a prolonged-release formulation of tacrolimus resulting in an extended oral absorption profile with an average time to C_{max} of approximately 2 hours. 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 was reduced when it was administered after a meal. Both the rate and extent of absorption of tacrolimus were reduced when administered with food. Bile flow does not influence the absorption of tacrolimus. A strong correlation exists between AUC and whole blood trough levels at steady-state for tacrolimus. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure. The mean AUC on day 1 was lower (± 54 to 80 %) when using an extended release tacrolimus compared to an immediate release formulation, but was similar after 14 days.

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

whole blood averaged 47,6 ℓ. Tacrolimus is a low-clearance medicine. In healthy subjects, the average total body clearance (TBC) 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 the medicine, 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.

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

Excretion
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.

Characteristics in patients:
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).

Variations with respect to confounding factors, age, polymorphism, metabolism and concomitant pathological situations (renal failure, hepatic insufficiency)
Based on preliminary clinical experience, the kinetic properties of tacrolimus are not altered in elderly patients.

Patients with liver dysfunction
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.

Patients with kidney dysfunction
Since tacrolimus is nearly completely metabolised, highly lipid-soluble, and has a molecular weight of 822 g/mol, 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.

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.

CONTRAINDICATIONS
- Known hypersensitivity to tacrolimus, the active ingredient in ADVAGRAF, or other macrolides.
- Hypersensitivity to any of the excipients of the capsules.
- Pregnancy and lactation (see Human Reproduction).

- As ADVAGRAF may alter the metabolism of oral contraceptives, other forms of contraception should be used.
- Concomitant administration of live attenuated vaccines.
- Concomitant administration with ciclosporin.
- Concomitant use with grapefruit juice.

WARNINGS AND SPECIAL PRECAUTIONS

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

ADVAGRAF therapy requires careful monitoring in units equipped and staffed with adequate laboratory and supportive medical resources. ADVAGRAF should only be prescribed and changes in immunosuppressive therapy, should only be initiated by medical practitioners experienced in immunosuppressive therapy and the management of transplant patients. The medical practitioner responsible for maintenance therapy should have complete information requisite for the follow-up of the patient. Dose and/or blood level adjustment, should only be undertaken by the transplant centre responsible for the transplant patient. Patients should be thoroughly controlled. In particular, during the first months post-transplant, close monitoring of the patient is required.

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

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

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) or other herbal preparations should be avoided when taking ADVAGRAF due to the risk of interactions that lead to decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus.

The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see Contraindications and Interactions).

High potassium intake or potassium-sparing diuretics should be avoided (see Interactions).

Certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see Interactions).
Nephrological adverse events can occur throughout the entire treatment period and, in the case of kidney transplant recipients, should be distinguished from symptoms of kidney graft rejection.

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.

Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of ADVAGRAF concentrations is recommended during episodes of diarrhoea.

Cardiac disorders
Cardiac hypertrophy or hypertrophy of the interventricular septum, reported as cardiomyopathies, has been observed, with ADVAGRAF blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients receiving immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at three months and then at 9-12 months). If abnormalities develop, dose reduction of ADVAGRAF therapy, or change of treatment to another immunosuppressive medicine should be considered.

ADVAGRAF may prolong the QT interval and may cause *Torsades de Pointes* Caution should be exercised in patients with risk factors for QT prolongation.

Lymphoproliferative disorders and malignancies
Patients treated with ADVAGRAF have been reported to develop Epstein-Barr Virus (EBV)-associated lymphoproliferative disorders. A combination of immunosuppressives such as antilymphocytic antibodies given concomitantly increases the risk of EBV-associated lymphoproliferative disorders. EBV-Viral Capsid Antigen (VCA)-negative patients have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with ADVAGRAF. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma.
In view of potential risk of malignancies, patients who spend extended periods in the sun, or are otherwise exposed to UV light, should apply a high protection sun-cream.

Patients treated with ADVAGRAF, are at increased risk of opportunistic infections (bacterial, mycobacterial, fungal, viral and protozoal). Among these conditions are BK virus (a member of the Polyomavirus family) associated nephropathy and John Cunningham (JC) virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that medical practitioners should consider in patients with deteriorating renal function or neurological symptoms.

Tuberculosis must be excluded prior to ADVAGRAF treatment.

Patients treated with ADVAGRAF have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking ADVAGRAF 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 ADVAGRAF is advised. Most patients completely recover after appropriate measures are taken.

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

Special populations
Dose reduction may be necessary in patients with severe liver impairment (see Dosage).

Excipients
As ADVAGRAF contains lactose, special care should be taken in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

The printing ink used to mark ADVAGRAF capsules contains soya lecithin. In patients who are hypersensitive to peanut or soya, the risk and severity of hypersensitivity should be weighed against the benefit of using ADVAGRAF.

Effects on ability to drive and use machines
ADVAGRAF is associated with visual and neurological disturbances. Patients treated with ADVAGRAF who are affected by such disorders should not drive a car or operate dangerous machines. This effect may be enhanced when ADVAGRAF is given together with alcohol.

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 substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels.

It is strongly recommended to closely monitor tacrolimus blood levels, as well as renal function and other side effects, whenever medicines which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly, and to interrupt or adjust the ADVAGRAF dose as appropriate in order to maintain similar tacrolimus exposure (see sections Dosage and Warnings and Special Precautions).

In vivo observations
Limited clinical data on medicine interactions are available. However, ADVAGRAF has been administered together with a great variety of other medicines in clinical trials.

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels
Clinically the following substances have been shown to increase tacrolimus blood levels:
Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin, HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir) or HCV protease inhibitors (e.g. telaprevir, boceprevir). Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients.
Pharmacokinetics studies have indicated that the increase in blood levels is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.
Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, amiodarone, danazol, ethinylestradiol, omeprazole, nefazodone.
In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethindrone, quinidine, tamoxifen, (triacetyl) oleandomycin.
Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.
Lansoprazole and ciclosporin may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

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

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

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

Effect of tacrolimus on the metabolism of other medicinal products
Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolised by CYP3A4 may affect the metabolism of such medicinal products.
The half-life of ciclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporin and tacrolimus is contraindicated and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see Dosage and Warnings and Special Precautions).
Tacrolimus has been shown to increase the blood level of phenytoin.
As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures.

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

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

As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g. amiloride, triamterene, or spironolactone) should be avoided (see Warnings and Special Precautions).

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 Contraindications).

HUMAN REPRODUCTION

Pregnancy

ADVAGRAF is contraindicated in pregnancy (see Contraindications). In animal studies (rats and rabbits), ADVAGRAF has been shown to be teratogenic at doses that also demonstrated maternal toxicity. Preclinical and human data show that ADVAGRAF is able to cross the placenta. The possibility of pregnancy should therefore be excluded before initiating ADVAGRAF therapy.

Lactation

Preclinical data in rats suggest that ADVAGRAF is excreted into breast milk. Human data on effects of ADVAGRAF during the lactation period are limited. As detrimental effects on the newborn cannot be excluded, women should not breastfeed whilst receiving ADVAGRAF.

Fertility

A negative effect of ADVAGRAF on male fertility in the form of reduced sperm counts and motility was observed in rats.

DOSAGE AND DIRECTIONS FOR USE

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 overimmunosuppression, 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. ADVAGRAF is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative transplant period. The ADVAGRAF dose may vary depending upon the immunosuppressive regimen chosen. ADVAGRAF dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring. If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.

Method of administration

It is recommended that the oral daily dose of ADVAGRAF be administered once daily in the morning. ADVAGRAF prolonged-release capsules should be taken immediately following removal from the blister. The capsules should be swallowed with fluid (preferably water).
ADVAGRAF should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption. If a patient recognises that he has forgotten to

take the morning dose, he should take his dose as soon as possible on the same day. He should not take a double dose the next morning.

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

Dosage recommendations - Conversion of immediate release formulation tacrolimus treated patients to ADVAGRAF
Allograft transplant patients maintained on twice daily tacrolimus immediate release formulation dosing requiring conversion to once daily ADVAGRAF may be converted on a 1:1 (mg/mg) total daily dose basis. ADVAGRAF 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.

Dosage 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 ADVAGRAF may need to be reduced.
For information on conversion from ciclosporin to ADVAGRAF, see below under DOSAGE ADJUSTMENTS IN SPECIFIC PATIENT POPULATIONS.

- **Kidney and liver transplantation**

For conversion from other immunosuppressants to once daily ADVAGRAF, treatment should begin with the initial oral dose recommended for primary immunosuppression.

- **Other allografts transplantation**

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

DOSAGE ADJUSTMENTS IN SPECIFIC PATIENT POPULATIONS

Patients with 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.
Patients with kidney impairment
As the pharmacokinetics of tacrolimus are unaffected by renal function, no dose adjustment should be required. However, owing to the nephrotoxic potential of ADVAGRAF careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

Race
In comparison to Caucasians, Black patients may require higher ADVAGRAF doses to achieve similar trough levels.
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 been established. Limited data are available but no recommendation on a dosage can be made.
Conversion from ciclosporin to ADVAGRAF
Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. ADVAGRAF therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, tacrolimus-based therapy has been initiated 12 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.

Various assays have been used to measure blood or plasma levels of ADVAGRAF. 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 ADVAGRAF is a medicinal product with low clearance, adjustments to the ADVAGRAF 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 study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels.
In clinical practice, whole blood trough levels have generally been in the range 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.

SIDE EFFECTS
The adverse events are listed below in descending order by frequency of occurrence:
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100);
rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Infections and infestations
Patients receiving ADVAGRAF are frequently at increased risk for infections (viral, bacterial, mycobacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.
Cases of BK virus (a member of the Polyomavirus family) 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 ADVAGRAF.

Neoplasms: benign, malignant and unspecified (incl. cysts and polyps)
Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including Epstein-Barr Virus (EBV)-associated lymphoproliferative disorders and skin malignancies have been reported in association with ADVAGRAF treatment.

Blood and lymphatic system disorders

common:	anaemia, leukopenia, thrombocytopenia, leukocytosis, abnormal red blood cell analyses
uncommon:	coagulopathies, abnormal coagulation and bleeding analyses, pancytopenia, neutropenia
rare:	thrombotic thrombocytopenic purpura, hypoprothrombinaemia
not known:	pure red cell aplasia, agranulocytosis, haemolytic anaemia

Immune system disorders
Allergic and anaphylactoid reactions have been observed in patients receiving ADVAGRAF (see Warnings and Special Precautions).

Endocrine disorders

rare:	hirsutism

Metabolism and nutrition disorders

very common:	hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common:	hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, decreased appetite, anorexia, metabolic acidoses,hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities
uncommon:	dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Psychiatric disorders

very common:	insomnia
common:	anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders
uncommon:	psychotic disorder

Nervous system disorders

very common:	tremor, headache
common:	seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, impaired writing, nervous system disorders
uncommon:	coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia
rare:	hypertonia
very rare:	myasthenia

Eye disorders

common:	blurred vision, photophobia, eye disorders
uncommon:	cataract
rare:	blindness

Ear and labyrinth disorders

common:	tinnitus
uncommon:	hypoacusis
rare:	neurosensory deafness

very rare:	impaired hearing

Cardiac disorders

common:	ischaemic coronary artery disorders, tachycardia
uncommon:	ventricular dysrhythmias and cardiac arrest, heart failure, cardiomyopathies, ventricular hypertrophy, supraventricular dysrhythmias, palpitations, abnormal ECG investigations, abnormal heart rate and pulse investigations
rare:	pericardial effusion
very rare:	abnormal echocardiogram, QT prolonged

Vascular disorders

very common:	hypertension
common:	haemorrhage, thrombembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
uncommon:	infarction, deep limb venous thrombosis, shock

Respiratory, thoracic and mediastinal disorders

common:	dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammation
uncommon:	respiratory failure, respiratory tract disorders, asthma
rare:	acute respiratory distress syndrome

Gastrointestinal disorders

very common:	diarrhoea, nausea
common:	gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms
uncommon:	paralytic ileus, peritonitis, acute and chronic pancreatitis, increased blood amylase, gastro-oesophageal reflux disease, impaired gastric emptying
rare:	subileus, pancreatic pseudocyst

Hepatobiliary disorders

very common:	abnormal liver function tests
common:	bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice
rare:	venoocclusive liver disease, hepatitic artery thrombosis
very rare:	hepatic failure

Skin and subcutaneous tissue disorders

common:	pruritus, rash, alopecia, acne, increased sweating
uncommon:	dermatitis, photosensitivity
rare:	toxic epidermal necrolysis (Lyell's syndrome)
very rare:	Stevens Johnson syndrome

Musculoskeletal and connective tissue disorders

common:	arthralgia, back pain, muscle spasms, pain in extremity
uncommon:	joint disorders

Renal and urinary disorders

very common:	renal impairment
common:	renal failure, acute renal failure, oliguria, renal tubular necrosis, toxic nephropathy, urinary abnormalities, bladder and urethral symptoms
uncommon:	anuria, haemolytic uraemic syndrome
very rare:	nephropathy, haemorrhagic cystitis

Reproductive system and breast disorders
uncommon: dysmenorrhoea, uterine bleeding

General disorders and administration site conditions
common: febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed,
uncommon: influenza like illness, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance
rare: fall, ulcer, chest tightness, thirst
very rare: fat tissue increased

Injury, poisoning and procedural complications
common: primary graft dysfunction

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Experience of overdosage is limited.
Earlier clinical experience (when initial induction doses were 2 or 3 times greater than those currently recommended) suggested that symptoms of overdosage may include renal, neurological and cardiac disturbances, glucose intolerance, hypertension and electrolyte disorders (e.g. hyperkalaemia). Over-immunosuppression may increase the risk for severe infections.
Liver function clearly influences all pre- and post-operative pharmacokinetic variables. Patients with failing liver grafts or those switched from other immunosuppressive therapy to ADVAGRAF should be monitored carefully to avoid overdosage.
No specific antidote to ADVAGRAF therapy is available. If overdosage occurs general supportive measures and symptomatic treatment should be conducted.
Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that ADVAGRAF will not be dialysable.
In isolated patients with very high plasma concentrations of tacrolimus, haemofiltration and haemodiafiltration have been reported to considerably decrease the tacrolimus levels.
In cases of oral intoxication, gastric lavage and/or the use of absorbents (such as activated charcoal) may be helpful.

IDENTIFICATION
ADVAGRAF 0,5 mg (Prolonged-Release Capsules)
ADVAGRAF 0,5 mg prolonged-release capsules are hard gelatin capsules (yellow-orange in colour) imprinted in red with 0.5 mg on the light yellow capsule cap and *647 on the orange capsule body, containing white powder.
ADVAGRAF 1 mg (Prolonged-Release Capsules)
ADVAGRAF 1 mg prolonged-release capsules are hard gelatin capsules are (white-orange in colour) imprinted in red with 1 mg on the white capsule cap and *677 on the orange capsule body, containing white powder.
ADVAGRAF 5 mg (Prolonged-Release Capsules)
ADVAGRAF prolonged-release capsules are hard gelatin capsules (greyish red-orange in colour) imprinted in red with 5 mg on the greyish red capsule cap and *687 on the orange capsule body, containing white powder.

PRESENTATION
ADVAGRAF 0,5 mg is supplied in transparent PVC/PVDC aluminium blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 30, 50 and 100 prolonged-release capsules are available.
ADVAGRAF 1 mg is supplied in transparent PVC/PVDC aluminium blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 30, 50, 60 and 100 prolonged-release capsules are available. Ten capsules per blister sheet.

ADVAGRAF 5 mg is supplied in transparent PVC/PVDC aluminium blisters containing 10 capsules within a protective foil wrapper, including a desiccant. Packs of 30, 50 and 100 prolonged-release hard capsules are available.

STORAGE INSTRUCTIONS
Store at or below 30 °C.
Keep out of reach of children.
Store in the original package and in a dry place in order to protect from light and moisture.

REGISTRATION NUMBERS

	South Africa:	**Namibia:**	**Kenya:**
ADVAGRAF 0,5 mg:	42/34/0786	Reg No. 13/34/0225	CTD2276
ADVAGRAF 1 mg:	42/34/0787	Reg No. 13/34/0226	CTD2275
ADVAGRAF 5 mg:	42/34/0788	Reg No. 13/34/0227	CTD2277

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Astellas Pharma (Pty) Ltd, 7 Mirage Road,Bedfordview, 2007, South Africa
Tel: +27 11 615 9433 Fax: +27 11 615 9427
Drugsafety.za@astellas.com

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