ADVAGRAF®

Tacrolimus (as monohydrate)

ACTION

At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of cytokine genes.

Tacrolimus is a highly potent immunosuppressive agent and has proven activity in both in vitro and in vivo experiments.

In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes, which are responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines (such as interleukins-2, -3, and γ-interferon) and the expression of the interleukin-2 receptor.

ABSORPTION

In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Available tacrolimus is generally rapidly absorbed. Advagraf is a prolonged-release formulation of tacrolimus resulting in an extended oral absorption profile with an average time to maximum blood concentration (Cmax) of approximately 2 hours (tmax). Absorption is variable and the mean oral bioavailability of tacrolimus (investigated with the Prograf formulation) is in the range of 20% - 25% (individual range in adult patients 6% - 43%). The oral bioavailability of Advagraf was reduced when it was administered after a meal. Both the rate and extent of absorption of Advagraf were reduced when administered with food. Bile flow does not influence the absorption of tacrolimus and therefore treatment with Advagraf may commence orally. A strong correlation exists between AUC and whole blood trough levels at steady-state for Advagraf. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

DISTRIBUTION

In man, the disposition of tacrolimus after intravenous infusion may be described as biphasic. In the systemic circulation, tacrolimus binds strongly to erythrocytes resulting in an approximate 20:1 distribution ratio of whole blood/plasma concentrations. In plasma, tacrolimus is highly bound (> 98.8%) to plasma proteins, mainly to serum albumin and 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.

METABOLISM

Tacrolimus is widely 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.

EXCRETION

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance estimated from whole blood concentrations was 2.25 l/h. In adult liver, 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.

INDICATIONS

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

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

DOSAGE AND ADMINISTRATION

Advagraf is a once-a-day oral formulation of tacrolimus. Advagraf therapy requires careful monitoring by adequately qualified and equipped personnel. This medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients. Inadvertent, unintentional or unsupervised switching of immediate- or prolonged-release formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of 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 drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

Posology

The recommended initial doses presented below are intended to act solely as a guideline. Advagraf is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The dose may vary depending upon the immunosuppressive regimen chosen. Advagraf dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring. If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered. In de novo kidney and liver transplant patients AUC0-24 of tacrolimus for Advagraf on Day 1 was 30% and 50% lower respectively, when compared with that for Prograf at equivalent doses. By Day 4, systemic exposure as measured by trough levels is similar for both kidney and liver transplant patients with both formulations. Careful and frequent monitoring of tacrolimus trough levels is recommended in the first two weeks post-transplant with Advagraf to ensure adequate drug exposure in the immediate post-transplant period. As tacrolimus is a substance with low clearance, adjustments to the Advagraf dose regimen may take several days before steady state is achieved.

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

Prophylaxis of kidney transplant rejection

Advagraf therapy should commence at a dose of 0.20 - 0.30 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery. Advagraf doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to Advagraf monotherapy. Post-transplant changes in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Prophylaxis of liver transplant rejection

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

Conversion of Prograf-treated patients to Advagraf

Allograft transplant patients maintained on twice daily Prograf capsules dosing requiring conversion to once daily Advagraf should be converted on a 1:1 (mg:mg) total daily dose basis. Advagraf should be administered in the morning. In stable patients converted from Prograf capsules (twice daily) to Advagraf (once daily) on a 1:1 (mg:mg) total daily dose basis, the systemic exposure to tacrolimus (AUC0-24) for Advagraf was approximately 10% lower than that for Prograf. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC0-24) for Advagraf is similar to that of Prograf. When converting from Prograf capsules to Advagraf, trough levels should be measured prior to conversion and within two weeks after conversion. Following conversion, tacrolimus trough levels should be monitored and if necessary dose adjustments made to maintain similar systemic exposure. Dose adjustments should be made to ensure that similar systemic exposure is maintained.

Conversion from ciclosporin to tacrolimus

Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. The combined administration of ciclosporin and tacrolimus is not recommended. Advagraf therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, tacrolimus-based therapy has been initiated 12 - 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected.

Treatment of allograft rejection

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

Treatment of allograft rejection after kidney or liver transplantation

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

Dose adjustments in special populations

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

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

Race: In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

Gender: There is no evidence that male and female patients require different doses to achieve similar trough levels.

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

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

Therapeutic drug monitoring

Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient aided by whole blood tacrolimus trough level monitoring. As an aid to optimise dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood. Comparisons of concentrations from the published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC 0-24) is similar between the two formulations Advagraf and Prograf.

Blood trough levels of tacrolimus should be monitored during the post-transplantation period. Tacrolimus blood trough levels should be determined approximately 24 hours post-dosing of Advagraf, just prior to the next dose. Frequent trough level monitoring in the initial two weeks post transplantation is recommended, followed by periodic monitoring during maintenance therapy. Blood trough levels of tacrolimus should also be closely monitored following conversion from Prograf to Advagraf, dose adjustments, changes in the immunosuppressive regimen, or co-administration of substances which may alter tacrolimus whole blood concentrations. The frequency of blood level monitoring should be based on clinical needs. As tacrolimus is a substance with low clearance, following adjustments to the Advagraf dose regimen it may take several days before the targeted steady state is achieved. Data from clinical studies suggest that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels. In clinical practice, whole blood trough levels have generally been in the range 5 - 20 ng/ml in liver transplant recipients and 10 - 20 ng/ml in kidney and heart transplant patients in the early post-transplant period. During subsequent maintenance therapy, blood concentrations have generally been in the range of 5 - 15 ng/ml in liver, kidney and heart transplant recipients.

Method of administration

Advagraf is a once-a-day oral formulation of tacrolimus. It is recommended that the oral daily dose of Advagraf be administered once daily in the morning. Advagraf prolonged-release hard capsules should be taken immediately following removal from the blister. Patients should be advised not to swallow the desiccant. The capsules should be swallowed whole with fluid (preferably water). Advagraf should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption. A forgotten morning dose should be taken as soon as possible on the same day. A double dose should not be taken on the next morning.

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

SPECIAL POPULATIONS

There is limited experience in non-Caucasian patients and patients at elevated immunological risk (e.g. retransplantation, evidence of panel reactive antibodies, PRA). Dose reduction may be necessary in patients with sever liver impairment. Advagraf capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. 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.

CONTRAINDICATIONS

Hypersensitivity to tacrolimus, or to any of the excipients.

Hypersensitivity to other macrolides.

WARNINGS AND PRECAUTIONS

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under- or over-exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist. Advagraf is not recommended for use in children below 18 years due to limited data on safety and/or efficacy. For treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients clinical data are not yet available for the prolonged-release formulation Advagraf. For prophylaxis of transplant rejection in adult heart allograft recipients clinical data are not yet available for Advagraf. During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered. When substances with a potential for interaction - particularly strong inhibitors of CYP3A4 (such as ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers of CYP3A4 (such as rifampin, rifabutin) - are being combined with tacrolimus, tacrolimus blood levels must be monitored to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure. Herbal preparations containing St. John's Wort (Hypericum perforatum) should be avoided when taking Advagraf due to the risk of interactions that lead to a decrease in both blood concentrations and the therapeutic effect of tacrolimus. 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. High potassium intake or potassium-sparing diuretics should be avoided. Certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects. 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 tacrolimus concentrations is recommended during episodes of diarrhoea.

Cardiac disorders

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed in Prograf treated patients on rare occasions and may also occur with Advagraf. Most cases have been reversible, occurring with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at 3 months and then at 9 -12 months). If abnormalities develop, dose reduction of Advagraf, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for causing Torsades de Pointes. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome.

Lymphoproliferative disorders and malignancies

Patients treated with tacrolimus have been reported to develop EBV-associated lymphoproliferative disorders. A combination of immunosuppressives such as antilymphocytic antibodies (e.g. basiliximab, daclizumab) given concomitantly increases the risk of EBV-associated lymphoproliferative disorders. EBV-Viral Capsid Antigen (VCA)-negative patients have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with Advagraf. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma. As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown. As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Patients treated with immunosuppressants, including Advagraf are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). Among these conditions are BK virus associated nephropathy and 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 physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Pure Red Cell Aplasia

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

DRUG INTERACTION

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 recommended to monitor tacrolimus blood levels whenever substances which have the potential to alter CYP3A metabolism or otherwise influence tacrolimus blood levels are used concomitantly, and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure. 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 or HIV protease inhibitors (e.g. ritonavir). 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, danazol, ethinylestradiol, omeprazole and 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. Lansoprazol 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 and cisapride), 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 not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin 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. 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.

Pregnancy and lactation

Pregnancy

Human data show that tacrolimus crosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse events on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women, when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus. In case of in utero exposure, monitoring of the newborn for the potential adverse events of tacrolimus is recommended (in particular effects on the kidneys). There is a risk for premature delivery (<37 week) (incidence of 66 of 123 births, i.e. 53.7%; however, data showed that the majority of the newborns had normal birth weight for their gestational age) as well as for hyperkalaemia in the newborn (incidence 8 of 111 neonates, i.e. 7.2 %) which, however normalises spontaneously. In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity.

Lactation

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

Fertility

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

Effects on ability to drive and use machines

Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if Advagraf is administered in association with alcohol. No studies on the effects of tacrolimus (Advagraf) on the ability to drive and use machines have been performed.

SIDE EFFECTS

The adverse reaction profile associated with immunosuppressive agents is often difficult to establish owing to the underlying disease and the concurrent use of multiple medicinal products. The most commonly reported adverse drug reactions (occurring in> 10% of patients) are tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension and insomnia. Many of the adverse reactions stated below are reversible and/or respond to dose reduction. The frequency of adverse reactions is defined as follows: very common (1/10); common (1/100 to < 1/10); uncommon (1/1,000 to < 1/100); rare (1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders
common: ischaemic coronary artery disorders, tachycardia
uncommon: heart failures, ventricular arrhythmias and cardiac arrest, supraventricular arrhythmias, cardiomyopathies, ECG investigations abnormal, ventricular hypertrophy, palpitations, heart rate and pulse investigations abnormal
rare: pericardial effusion
very rare: echocardiogram abnormal
Blood and lymphatic system disorders
common: anaemia, thrombocytopenia, leukopenia, red blood cell analyses abnormal, leukocytosis
uncommon: coagulopathies, pancytopenia, neutropenia, coagulation and bleeding analyses, abnormal
rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia
not known: pure red cell aplasia, agranulocytosis, haemolytic anaemia
Nervous system disorders
very common: headache, tremor
common: nervous system disorders seizures, disturbances in consciousness, peripheral neuropathies, dizziness, paraesthesias and dysaesthesias, writing impaired
uncommon: encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, speech and language abnormalities, paralysis and paresis, amnesia
rare: hypertonia
very rare: myasthenia
Eye disorders
common: eye disorders, vision blurred, photophobia
uncommon: cataract
rare: blindness
Ear and labyrinth disorders
common: tinnitus
uncommon: hypoacusis
rare: deafness neurosensory
very rare: hearing impaired
Respiratory, thoracic and mediastinal disorders
common: parenchymal lung disorders, dyspnoea, pleural effusion, cough, pharyngitis, nasal congestion and inflammations
uncommon: respiratory failures, respiratory tract disorders, asthma
rare: acute respiratory distress syndrome
Gastrointestinal disorders
very common: diarrhoea, nausea
common: gastrointestinal signs and symptoms, vomiting, gastrointestinal and abdominal pains, gastrointestinal inflammatory conditions, gastrointestinal haemorrhages, gastrointestinal ulceration and perforation, ascites, stomatitis and ulceration, constipation, dyspeptic signs and symptoms, flatulence, bloating and disturbances in bowel stools
uncommon: acute and chronic pancreatitis, peritonitis, blood amylase increased, ileus paralytic, gastrooesophageal reflux disease, impaired gastric emptying
rare: pancreatic pseudocyst, subileus
Renal and urinary disorders
very common: renal impairment
common: renal failure, renal failure acute, nephropathy toxic, renal tubular necrosis, urinary abnormalities, oliguria, bladder and urethral symptoms
uncommon: haemolytic uraemic syndrome, anuria
very rare: nephropathy, cystitis haemorrhagic
Skin and subcutaneous tissue disorders
common: rash, pruritus, alopecias, acne, sweating increased
uncommon: dermatitis, photosensitivity
rare: toxic epidermal necrolysis (Lyell's syndrome)
very rare: Stevens Johnson syndrome
Musculoskeletal and connective tissue disorders
common: arthralgia, back pain, muscle cramps, pain in limb
uncommon: joint disorders
Endocrine disorders
rare: hirsutism
Metabolism and nutrition disorders
very common: diabetes mellitus, hyperglycaemic conditions, hyperkalaemia
common: anorexia, metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypophosphataemia
uncommon: dehydration, hypoglycaemia, hypoproteinaemia, hyperphosphataemia
Infections and infestations
As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.
Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Advagraf.
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).
Neoplasms benign, malignant and unspecified
Patients receiving immunosuppressive therapy 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.
Vascular disorders
very common: hypertension
common: thromboembolic and ischaemic events, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders
uncommon: venous thrombosis deep limb, shock, infarction
General disorders and administration site conditions
common: febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed, blood alkaline phosphatase increased, weight increased
uncommon: weight decreased, influenza like illness, blood lactate dehydrogenase increased, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance
rare: fall, ulcer, chest tightness, mobility decreased, thirst
very rare: fat tissue increased
Immune system disorders
Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus.
Hepatobiliary disorders
very common: liver function tests abnormal
common: bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice
rare: venoocclusive liver disease, hepatitic artery thrombosis
very rare: hepatic failure
Reproductive system and breast disorders
uncommon: dysmenorrhoea and uterine bleeding
Psychiatric disorders
very common: insomnia
common: confusion and disorientation, depression, anxiety symptoms, hallucination, mental disorders, depressed mood, mood disorders and disturbances, nightmare
uncommon: psychotic disorder

OVERDOSAGE

Experience with overdose is limited. Several cases of accidental overdose have been reported with tacrolimus; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy and increases in blood urea nitrogen, serum creatinine and alanine aminotransferase levels. No specific antidote to tacrolimus therapy is available. If overdose occurs, general supportive measures and symptomatic treatment should be conducted. Based on its high molecular weight, poor aqueous solubility, and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus will not be dialysable. In isolated patients with very high plasma levels, haemofiltration or -dialfiltration have been effective in reducing toxic concentrations. In cases of oral intoxication, gastric lavage and/or the use of adsorbents (such as activated charcoal) may be helpful, if used shortly after intake.

PRESENTATIONS

Prolonged-release hard capsules

ADVAGRAF 0.5 mg:	Tacrolimus (as monohydrate) 0.5 mg/capsule
ADVAGRAF 1 mg:	Tacrolimus (as monohydrate) 1 mg/capsule
ADVAGRAF 3 mg:	Tacrolimus (as monohydrate) 3 mg/capsule
ADVAGRAF 5 mg:	Tacrolimus (as monohydrate) 5 mg/capsule

Capsule content: *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 (Opacode S-1-15083): *Shellac, Lecithin (soya), Simeticone, Red iron oxide (E 172), Hydroxypropylcellulose.*

Council of Arab Health Ministers, Union of Arab Pharmacists

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Manufactured by:
Astellas Ireland Co. Ltd.
Killorglin, Co. Kerry, Ireland
for
HIKMA Pharmaceuticals,
Amman - Jordan

Keep medicament out of the reach of children

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