CLEAN PROPOSED PROFESSIONAL INFORMATION

WARNINGS

Malignancies and serious infections: Increased risk for developing serious infections and malignancies with tacrolimus or other immunosuppressants that may lead to hospitalisation or death (see section 4.4)

Extended-release formulations of tacrolimus are not interchangeable with immediate release formulations of tacrolimus without careful monitoring and supervision by a transplant specialist.

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

GRAFOLIN 0,5 mg capsules

GRAFOLIN 1 mg capsules

GRAFOLIN 5 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

GRAFOLIN 0,5 mg

Each capsule contains 0,5 mg tacrolimus monohydrate.

Contains sugar: lactose monohydrate 60,50 mg per capsule.

GRAFOLIN 1 mg

Each capsule contains 1 mg tacrolimus monohydrate.

Contains sugar: lactose monohydrate 59,40 mg per capsule.

GRAFOLIN 5 mg

Each capsule contains 5 mg tacrolimus monohydrate.

Contains sugar: lactose monohydrate 131,20 mg per capsule.

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For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules

GRAFOLIN 0,5 mg:

White to off white powder filled in size 5 hard gelatin capsules with red opaque cap and red opaque body printed SAL on cap and 720 on body.

GRAFOLIN 1 mg:

White to off white powder filled in size 5 hard gelatin capsules with green opaque cap and green opaque body printed SAL on cap and 721 on body.

GRAFOLIN 5 mg:

White to off white powder filled in size 4 hard gelatin capsules with teal opaque cap and teal opaque body printed SAL on cap and 722 on body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary immunosuppression in liver and kidney allograft recipients and liver, kidney, or heart allograft rejection resistant to conventional immunosuppressive regimens.

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 lake place under the close supervision of a transplant specialist. Following conversion to any alternative formulation, therapeutic medicine

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monitoring must be performed, and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

Absorption of orally administered tacrolimus in the immediate post-operative period in heart transplant patients is problematic and creates difficulties in designing a suitable dosing regimen. Therefore, initiation of tacrolimus therapy via the intravenous route and conversion to oral dosing, when possible, or initiating GRAFOLIN orally following antibody induction therapy are the two preferable options for use of GRAFOLIN in heart transplant patients.

General statement

The dosage recommendations given below are intended to act as a guideline. GRAFOLIN doses should be adjusted according to individual patient requirements.

If the clinical condition of the patient allows oral dosing, administration of oral GRAFOLIN should start as soon as practicable. In some liver transplantation patients, therapy has commenced orally by administering the capsule contents suspended in water via an intranasal gastric tube.

GRAFOLIN is normally administered together with other immunosuppressive medicine. In isolated cases, successful maintenance therapy with GRAFOLIN alone has also been described. GRAFOLIN should not be given together with ciclosporin (see section 4.3). If allograft rejection or adverse events occur, alteration in the immunosuppressive regimen should be considered.

Duration and onset of intake

For onset of treatment see above. To suppress graft rejection, the capsules normally have to be taken continuously. Therefore, no limitation of duration can be given.

Maintenance therapy in liver and kidney transplant recipients (adults and children)

General considerations

Continuous immunosuppression with GRAFOLIN is recommended to maintain graft survival.

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If progression of disease occurs (e.g., signs of acute rejection), alteration of the immunosuppressive regimen should be considered. Increase in the amount of corticosteroids, introduction of short courses of monoclonal antibodies and increase in the dose of GRAFOLIN have all been used to manage rejection episodes.

If signs of toxicity are noted, the dose of GRAFOLIN should be reduced. Patients should be instructed not to decrease the dose without the consent of the treating medical practitioner. During the course of the post-transplant improvement of the patient, it is likely that the pharmacokinetics of GRAFOLIN may be altered, requiring adjustment of the GRAFOLIN dose.

Primary immunosuppression - adult patients

Liver transplantation

Patients should be converted from intravenous to oral medication as soon as the individual circumstances permit.

Oral administration

Initially an oral dose in a range from 0,10 to 0,20 mg/kg/day should be administered in two divided doses. Initial oral doses have been administered in a range from 0,02 to 0,30 mg/kg/day.

Kidney transplantation

Initial administration

Initially, an oral dose in a range from 0,15 to 0,40 mg/kg/day should be administered in two divided doses.

Primary immunosuppression dose levels - paediatric patients

Paediatric patients generally require doses 1½ to 2 times higher than the recommended adult doses to achieve the same blood levels Experience with initial oral administration in paediatric patients is limited.

Liver and kidney transplantation

An initial dose of 0,30 mg/kg/day for liver and kidney transplantation should be administered

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in two divided doses.

Maintenance therapy with GRAFOLIN in liver or kidney transplant recipients

It is necessary to continue immunosuppression with GRAFOLIN to maintain graft survival. Dosage recommendations should be based on individual patient experience (see introductory remarks above). There is a trend towards the use of lower doses of GRAFOLIN during maintenance therapy. Dosing should be primarily based on clinical assessments of rejection and tolerability.

Rescue therapy with GRAFOLIN

In patients experiencing rejection episodes that are unresponsive to conventional immunosuppressive therapy, GRAFOLIN treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.

The combined administration of ciclosporin and GRAFOLIN is not recommended as GRAFOLIN may increase the half-life of ciclosporin and exacerbate any toxic effects (see section 4.5). Therefore, care should be taken when converting patients from ciclosporin to GRAFOLIN-based therapy. It is recommended that ciclosporin blood levels are monitored prior to the administration of GRAFOLIN. The most appropriate time to initiate GRAFOLIN therapy should be based upon information on ciclosporin blood levels and the clinical condition of the patient. Dosing may be delayed in the presence of elevated ciclosporin levels e.g., in patients experiencing renal failure. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin may be affected.

Heart allograft rejection

An initial oral dose of 0,30 mg/kg/day should be administered in two divided doses (e.g., morning and evening).

DOSAGE ADJUSTMENTS IN SPECIFIC PATIENT POPULATIONS

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Patients with liver impairment

A dose reduction may be necessary in patients with pre- and/or post-operative impairment, e.g., early graft dysfunction.

Patients with renal impairment

No adjustment in dose is regarded as necessary on pharmacokinetic principles. However, careful monitoring of renal function, including serial creatinine estimations, calculations of creatinine clearance and monitoring of urine output, is recommended.

Elderly patients

There is no evidence presently available to suggest that doses should be altered in elderly patients.

Paediatric patients

The safety and efficacy of GRAFOLIN 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 GRAFOLIN

Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. GRAFOLIN 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, GRAFOLIN 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.

Whole blood concentration monitoring

Various assays have been used to measure blood or plasma levels of GRAFOLIN. Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters

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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 lubes 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 lie kept longer, they should be deep frozen at -20 °C tor up to 12 months, GRAFOLIN whole blood trough levels should be monitored periodically during maintenance therapy. The frequency of blood level monitoring should be based on clinical needs, but in general, because of its long half-life, it is unnecessary to measure blood levels on a daily basis. Medicine level monitoring (therapeutic outcomes monitoring - TOM) is recommended during the early post-transplantation period, following dose adjustment, after switching from another immunosuppressive regimen. and following co-administration of medicines which are likely to lead to interactions.

Clinical experience suggests that the majority of patients can be successfully managed if the blood concentrations of GRAFOLIN are maintained below 25 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood level concentrations. If the blood levels are below the limit of quantification of the assay and the patient's clinical condition is satisfactory, then the dose should not be adjusted.

Method of administration

It is recommended that the oral daily dose should be taken in two divided doses. The capsules should be swallowed with fluid, preferably water. Based on pharmacokinetic considerations, the capsules should be taken on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal to achieve maximal absorption (see sections 4.4 and 5.2). The capsules should

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be taken out of the blister only immediately before intake. After opening the aluminium wrapper, the capsules from the blisters must be used within 12 months.

4.3 Contraindications

- Hypersensitivity to tacrolimus, other macrolides or to any of the excipients (see section 6.1)
- Pregnancy and lactation (see section 4.6).
- As GRAFOLIN 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. (see section 4.6).

4.4 Special warnings and precautions for use

Not interchangeable with extended-release tacrolimus products medication errors

Medication errors, including substitution and dispensing errors, between tacrolimus immediate release products and tacrolimus extended-release products were reported. This led to serious adverse reactions, including graft rejection, or other adverse reactions due to under-or overexposure to tacrolimus. Tacrolimus is not interchangeable or substitutable for tacrolimus extended-release products. (see Boxed Warning). Changes between tacrolimus immediate release and extended-release dosage forms must occur under physician supervision. Instruct patients and caregivers to recognize the appearance of tacrolimus dosage forms (see section 2) and to confirm with the healthcare provider if a different medicine is dispensed.

GRAFOLIN therapy requires careful monitoring in units equipped and staffed with adequate laboratory and supportive medical resources. GRAFOLIN should only be prescribed and changes in immunosuppressive therapy, should only be initiated by medical practitioners

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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.

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

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) or other herbal preparations should be avoided when taking GRAFOLIN 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 section 4.5).

High potassium intake or potassium-sparing diuretics should be avoided (see section 4.5).

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

Lymphoma and other malignancies

Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see Boxed Warning). The risk appears to be related to the intensity and duration of immunosuppression rather than

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to the use of any specific medicine.

As usual for patients with increased risk for skin cancer, examine patients for skin changes; exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen with a high protection factor.

Post-transplant lymphoproliferative disorder (PTLD) has been reported in immunosuppressed organ transplant recipients. The majority of PTLD events appear related to Epstein-Barr Virus (EBV) infection. The risk of PTLD appears greatest in those individuals who are EBV seronegative, a population which includes many young children. Monitor EBV serology during treatment.

Serious infections

Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Serious viral infections reported include:

- Polyoma virus-associated nephropathy (PVAN), mostly due to BK virus infection.
- JC virus-associated progressive multifocal leukoencephalopathy (PML).
- Cytomegalovirus infections: CMV seronegative transplant patients who receive an organ from a CMV seropositive donor disease are at higher risk of developing CMV viremia and CMV disease.

Monitor for the development of infection and adjust the immunosuppressive regimen to balance the risk of rejection with the risk of infection (see section 4.8).

Tuberculosis must be excluded prior to GRAFOLIN treatment.

New onset diabetes after transplant

Tacrolimus was shown to cause new onset diabetes mellitus in clinical trials of kidney, liver, and heart transplantation. New onset diabetes after transplantation may be reversible in some patients. African-American and Hispanic kidney transplant patients are at an increased risk.

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Blood glucose concentrations should be monitored closely in patients using GRAFOLIN (see section 4.8).

Nephrotoxicity

Tacrolimus, like other calcineurin inhibitors, can cause acute or chronic nephrotoxicity. Nephrotoxicity was reported in clinical trials (see section 4.8). Consider dosage reduction in patients with elevated serum creatinine and tacrolimus whole blood trough concentrations greater than the recommended range. The risk for nephrotoxicity may increase when tacrolimus is concomitantly administered with CYP3A inhibitors (by increasing tacrolimus whole blood concentrations) or medicines associated with nephrotoxicity (e.g., aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors, protease inhibitors) (see section 4.5]. Monitor renal function and consider dosage reduction if nephrotoxicity occurs.

Neurotoxicity

Tacrolimus may cause a spectrum of neurotoxicities. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremors, paraesthesia, headache, mental status changes, and changes in motor and sensory functions (see section 4.8). As symptoms may be associated with tacrolimus whole blood trough concentrations at or above the recommended range, monitor for neurologic symptoms and consider dosage reduction or discontinuation of GRAFOLIN if neurotoxicity occurs.

Hyperkalaemia

Hyperkalaemia has been reported with tacrolimus use. Serum potassium levels should be monitored. Careful consideration should be given prior to use of other medicine also associated with hyperkalaemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) during tacrolimus therapy (see section 4.8). Monitor serum potassium levels

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periodically during treatment.

Hypertension

Hypertension is a frequent adverse effect of tacrolimus therapy and may require antihypertensive therapy (see section 4.8). The control of blood pressure can be accomplished with any of the common antihypertensive medicine, though careful consideration should be given prior to use of antihypertensive medicine associated with hyperkalaemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) (see section 4.4). Calcium-channel blocking medicine may increase tacrolimus blood concentrations and therefore require dosage reduction of GRAFOLIN (see section 4.5).

Not recommended for use with sirolimus

GRAFOLIN is not recommended for use with sirolimus:

- The use of sirolimus with tacrolimus in studies of de novo liver transplant patients was associated with an excess mortality, graft loss, and hepatic artery thrombosis (HAT) and is not recommended.
- The use of sirolimus (2 mg per day) with tacrolimus in heart transplant patients was associated with increased risk of renal function impairment, wound healing complications, and insulin-dependent post-transplant diabetes mellitus, and is not recommended.

Interactions with CYP3A4 Inhibitors and Inducers

When co-administering tacrolimus with strong CYP3A4 inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong inducers (e.g., rifampin, rifabutin), adjustments in the dosing regimen of tacrolimus and subsequent frequent monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions.

QT prolongation

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Tacrolimus may prolong the QT/QTc interval and may cause *Torsade de Pointes*. Avoid tacrolimus in patients with congenital long QT syndrome. In patients with congestive heart failure, bradydysrhythmias, those taking certain antidysrhythmic medications or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnaesemia, consider obtaining electrocardiograms and monitoring electrolytes (magnesium, potassium, calcium) periodically during treatment.

When co-administering tacrolimus with other substrates and/or inhibitors of CYP3A4 that also have the potential to prolong the QT interval, a reduction in tacrolimus dose, frequent monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended. Use of tacrolimus with amiodarone has been reported to result in increased tacrolimus whole blood concentrations with or without concurrent QT prolongation (see section 4.5).

Myocardial hypertrophy

Myocardial hypertrophy has been reported in infants, children, and adults, particularly those with high tacrolimus trough concentrations, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving tacrolimus therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of GRAFOLIN should be considered (see section 4.8).

Immunisations

Whenever possible, administer the complete complement of vaccines before transplantation and treatment with GRAFOLIN. The use of live vaccines should be avoided during treatment with GRAFOLIN; examples include (not limited to) the following: intranasal influenza, measles,

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mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines. Inactivated vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic during treatment with GRAFOLIN.

Pure red cell aplasia

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. A mechanism for tacrolimus induced PRCA has not been elucidated. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. If PRCA is diagnosed, discontinuation of GRAFOLIN should be considered (see section 4.8).

Contains lactose monohydrate

GRAFOLIN contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions of galactose intolerance total lactase deficiency, glucose-galactose malabsorption should not take GRAFOLIN.

4.5 Interaction with other medicines and other forms of interaction

Mycophenolic acid

When tacrolimus is prescribed with a given dose of a mycophenolic acid (MPA), exposure to MPA is higher with tacrolimus co-administration with MPA than with ciclosporin co-administration because ciclosporin interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Monitor for MPA associated adverse reactions and reduce the dose of concomitantly administered mycophenolic acid medicines as needed.

Effect of other medicines on tacrolimus

Table 1 displays the effects of other medicines on tacrolimus

Table 1: Effects of Other Medicines /Substances on Tacrolimus *

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Medicine/substance class or name	**Interaction effect**	**Recommendations**
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.
Strong CYP3A inducers‡: Antimycobacterials (e.g., rifampin, rifabutin), anticonvulsants (e.g., phenobarbitone), St John's Wort	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection (see section 4.4).	Increase tacrolimus dose and monitor tacrolimus whole blood trough concentrations (see section 4.2).
Strong CYP3A inhibitors‡: Protease inhibitors (e.g., nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol),	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) (see section 4.4).	Reduce tacrolimus dose (for give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations (see section 4.2).

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Medicine/substance class or name	**Interaction effect**	**Recommendations**
nefazodone, S*chisandra sphenanthera* extracts.		
Mild or moderate CYP3A Inhibitors: Clotrimazole, antibiotics (e.g., erythromycin, fluconazole), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl oestradiol, cimetidine, lansoprazole, and omeprazole.	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).
Other medicines, such as: Magnesium and aluminium hydroxide antacids, metoclopramide	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).
Mild or moderate CYP3A inducers, methylprednisolone,	May decrease tacrolimus concentrations.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose

Medicine/substance class or name	Interaction effect	Recommendations
prednisone		if needed (see section 4.2).

*Tacrolimus dosage adjustment recommendation based on observed effect of co-administered medicine on tacrolimus exposures, literature reports of altered tacrolimus exposures, or the other medicine's known CYP3A inhibitor/inducer status.

†High dose or double strength grapefruit juice is a strong CYP3A inhibitor; low dose or single strength grapefruit juice is a moderate CYP3A inhibitor.

‡Strong CYP3A inhibitor/inducer, based on reported effect on exposures to tacrolimus along with supporting *in vitro* CYP3A inhibitor/inducer data, or based on medicine-medicine interaction studies with midazolam (sensitive CYP3A probe substrate).

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.

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.

Immunosuppressants may affect the response to vaccination and vaccination during treatment

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with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

GRAFOLIN is contraindicated in pregnancy (see section 4.3). In animal studies (rats and rabbits), tacrolimus 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 therefore be excluded before initiating GRAFOLIN therapy.

Breastfeeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

The adverse event profile associated with immunosuppressive medicine is often difficult to establish owing to the underlying disease and the concurrent use of multiple medicines. There is evidence that some of the events stated below are reversible and respond to dose reduction.

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Oral administration appears to be associated with a lower incidence of adverse events compared with intravenous use.

b. Tabulated summary of adverse reactions

The following adverse reactions were reported during clinical studies and/or post-marketing use:

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Increased risk tor infections (viral, bacterial,mycobacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur (see section 4.4)
	Frequency unknown	Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal; -polyoma virus-associated nephropathy, (PVAN) including graft loss (see section 4.4)
Neoplasms: benign. malignant and unspecified (incl. cysts and polyps)	Less frequent	Increased risk of developing malignancies. Benign as well as malignant neoplasms includin[redacted] Epstein-Barr Virus (EBV)-ass[redacted] lymphoproliferative disorders and skin malignancies (see section 4.4) have been reported

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MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Frequent	Anaemia, leukopenia, thrombocylopenia, leukocytosis, abnormal red blood cell analyses
	Less frequent	Coagulopathies, abnormal coagulation and bleeding analyses, pancytopenia, neutropenia, thrombotic thrombocytopenic purpura, hypoprothrombinaemia (see section 4.4)
	Frequency unknown	Agranulocytosis, disseminated intravascular coagulation, haemolytic anaemia, pure red cell aplasia (see section 4.4)
Immune system disorders	Less frequent	Allergic and anaphylactoid reactions
Endocrine disorders	Less frequent	Hirsutism
Metabolism and nutrition disorders	Frequent	Hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, decreased appetite, anorexia, metabolic acidosis, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte

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MedDRA system organ class	Frequency	Adverse reactions
		abnormalities
	Less frequent	Dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia
	Frequency unknown	Glycosuria, increased amylase including pancreatitis, weight decreased
Psychiatric disorders	Frequent	Insomnia, anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders
	Less frequent	Psychotic disorder
Nervous system disorders	Frequent	Tremor, headache, seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, impaired writing, nervous system disorders
	Less frequent	Coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia, hypertonia, myasthenia

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Frequency unknown	Carpal tunnel syndrome, cerebral infarction, hemiparesis, leukoencephalopathy, mental disorder, mutism, posterior reversible encephalopathy syndrome (PRES) (see section 4.4), progressive multifocal leukoencephalopathy (PML) (see section 4.4), quadriplegia, syncope
Eye disorders	Frequent	Blurred vision, pholophobia, eye disorders
	Less frequent	Cataract, blindness
Ear and labyrinth disorders	Frequent	Tinnitus
	Less frequent	Hypoacusis, neurosensory deafness, impaired hearing
Cardiac disorders	Frequent	Ischaemic coronary artery disorders, tachycardia
	Less frequent	Ventricular dysrhythmias and cardiac arrest, heart failure, cardiomyopathies, ventricular hypertrophy, supraventricular dysrhythmias, palpitations, abnormal ECG investigations, abnormal heart rate and pulse investigations; pericardial effusion, abnormal echocardiogram

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Frequency unknown	Atrial fibrillation, atrial flutter, electrocardiogram T wave abnormal, flushing, pericardial effusion, QT prolongation, Torsade de Pointes, ventricular extrasystoles, ventricular fibrillation (see section 4.4)
Vascular disorders	Frequent	Hypertension, haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
	Less frequent	Myocardial infarction, deep vein thrombosis shock, myocardial ischaemia, myocardial hypertrophy
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammation
	Less frequent	Respiratory failure, acute respiratory distress syndrome, respiratory tract disorders, asthma
	Frequency unknown	Interstitial lung disease, lung infiltration
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, gastrointestinal inflammatory conditions, gastrointestinal ulceration and

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MedDRA system organ class	Frequency	Adverse reactions
		perforation, gastrointestinal haemorrhages, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms, stomatitis and ulceration
	Less frequent	Paralytic ileus, peritonitis, acute and chronic pancreatitis, increased blood amylase, gastro-oesophageal reflux disease, impaired gastric emptying, subileus, pancreatic pseudocyst
	Frequency unknown	Colitis, enterocolitis, gastroenteritis, pancreatitis haemorrhagic, pancreatitis necrotising
Hepato-biliary disorders	Frequent	Hepatic enzymes and function abnormalities, cholestasis and jaundice, heptocellular damage and hepatitis, cholangitis
	Less frequent	Hepatic artery thrombosis, veno-occlusive liver disease, hepatic failure, bile duct stenosis
	Frequency unknown	Hepatic cytolysis, hepatic necrosis, hepatotoxicity, liver fatty

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MedDRA system organ class	**Frequency**	**Adverse reactions**
Skin and subcutaneous tissue disorders	Frequent	Pruritus, rash, alopecia, acne, increased sweating
	Less frequent	Dermatitis, photosensitivity, toxic epidermal necrolysis (Lyell's syndrome), Stevens Johnson syndrome
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, muscle cramps, pain in limb, back pain
	Less frequent	Joint disorders
	Frequency unknown	Pain in extremity including Calcineurin-Inhibitor Induced Pain Syndrome (CIPS).
Renal and urinary disorders	Frequent	Acute renal failure, renal impairment, renal failure, oliguria, renal tubular necrosis, toxic nephropathy, urinary abnormalities, bladder and urethral symptoms
	Less frequent	Haemolytic uraemic syndrome, haemorrhagic cystitis, nephropathy, anuria
Reproductive system and breast disorders	Less frequent	Dysmenorrhoea and uterine bleeding
General disorders and administration site conditions	Frequent	Disturbed body temperature perception, asthenic conditions, febrile disorders, oedema, pain and

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MedDRA system organ class	**Frequency**	**Adverse reactions**
		discomfort, increased blood alkaline phosphatase, increased weight
	Less frequent	Feeling jittery, multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling abnormal, increased blood lactate dehydrogenase, decreased weight, thirst, fall, chest tightness, decreased mobility, ulcer, increased fat tissue
	Frequency unknown	Hot flushes
Investigations	Frequency unknown	Regular 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
Injury, poisoning and procedural complications	Frequent	Primary graft dysfunction, medication errors, including inadvertent, unintentional or unsupervised substitution of

MedDRA system organ class	Frequency	Adverse reactions
		immediate- or extended-release tacrolimus formulations, have been observed (see 4.4).
	Frequency unknown	A number of associated cases of transplant rejection have been reported

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. Health care 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 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 GRAFOLIN should be monitored carefully to avoid overdosage.

No specific antidote to GRAFOLIN 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,

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it is anticipated that GRAFOLIN 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, the use of absorbents (such as activated charcoal) may be helpful.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcineurin inhibitors ATC Code: L04AD02

Mechanism of action

Tacrolimus is an immunosuppressive medicine with activity in both *in vitro* and *in vivo* experiments. In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes that are mainly responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependant 8-cell proliferation, as well as the formation of lymphokines such as interteukin-2, -3 and y-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

General characteristics

Absorption

In the rat, the major site of absorption was identified as the upper gastrointestinal tract. Absorption of tacrolimus is incomplete and highly variable following oral administration. After oral administration, tacrolimus is rapidly absorbed in some patients with peak plasma concentrations reached within 0,5 hours to 3 hours, while in other patients it appears to be continuously absorbed over a prolonged period yielding a relatively flat absorpti:on profile. Poor dissolution of tacrolimus in gastric fluids resulting from low aqueous solubility and alterations in gastric motility may be partially responsible for this observation.

In kidney allograft patients, single oral doses of 0,10; 0,15 and 0,2 mg/kg resulted in peak

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blood concentrations of 19,2; 24,2; and 47,9 ng/ml, respectively. The times to reach peak concentration varied from 0,7 to 6 hours.

The mean bioavailability of tacrolimus capsules was estimated to be 21,8 % in liver transplant patients, 20,1 % in kidney transplant patients, 14,4 to 17,4 % in healthy subjects and 25 % in paediatric liver transplant patients.

In heart allograft recipients, tacrolimus is absorbed with a mean time to peak concentration (t_{max}) of approximately 1,5 hours. The oral bioavailability of tacrolimus averages 20 %, however there is a high degree of patient variability in heart transplant patients.

The oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat content. There was a decrease in AUC (plasma 27 %, whole blood 35 %), C_{max} (plasma 50 %, whole blood 57 %), and an increase in t_{max} (both plasma and whole blood 173 %). Both rate and extent of absorption were reduced when tacrolimus was given with food.

Bile does not influence the absorption of tacrolimus, and therefore commencement of tacrolimus therapy with an oral dose and early conversion of liver transplant patients to oral therapy is possible.

Distribution and elimination

Distribution of tacrolimus is extensive. It is highly bound to red blood cells and to plasma proteins. Following intravenous infusion of tacrolimus, peak plasma concentrations are reached at the end of the infusion. Concentration declines rapidly after the end of infusion indicating rapid distribution of the medicine outside the plasma compartment. Once distribution equilibrium is reached, tacrolimus concentrations decline at a slower rate, corresponding to the disposition of the medicine.

The pharmacokinetics of tacrolimus after intravenous infusion to transplant patients may be described by a two-compartment model. In kidney transplant patients, the increase in AUC and C_{max} after single oral dose post-transplant was proportional to the increase in oral dose. In liver transplant patients, the mean trough level concentrations of tacrolimus remained relatively stable up to 6 months post-transplant. Based on plasma level data in transplant patients, the volume of distribution averaged 1342 l, suggesting extensive distribution of

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tacrolimus in the body. In liver transplant patients, the volume of distribution averaged 64,4 l based on whole blood concentrations (0,85 l/kg when normalised to body weight) and 1094,5 l based on the plasma concentrations (150,1 l/h or 2,0 l/h/kg when normalised to body weight). Measurement of minimum blood or plasma levels, which were correlated with AUC, provided an accurate reflection of total tacrolimus exposure.

Tacrolimus is highly bound to plasma proteins (> 98,8 %) in rat, dog, monkey and man. The whole blood/plasma ratio appears to be approximately 20:1 (volunteer studies). Tacrolimus binds strongly to erythrocytes. This effect is dependent on temperature, lower temperatures resulting in lower plasma concentrations. After oral administration (0,15 mg/kg twice daily) to liver transplant patients. steady-state concentrations of tacrolimus were achieved within 3 days in most patients. The half-life of tacrolimus is long and variable, and clearance low. The average total body clearance amounts to approximately 30 ml/min/g (7 - 103 ml/min/kg). In liver transplant patients, the total body clearance observed was 4,5 l/h (whole blood concentration) and 150,1 l/h or 2,0 l/h/kg when normalised to body weight (plasma concentrations).

The plasma half-life of tacrolimus ranges between 3,5 and 40,5 h in renal transplant patients, other references stating up to 50 h. In liver transplant patients, the elimination half-life based on the whole blood concentration averaged 11,7 h (range 6,1 - 20,9 h) and based on the plasma concentration 6,5 h (range 2,7 - 13,3 h). The renal clearance is less than 1 ml/min. The metabolites of tacrolimus are primarily excreted via the bile. The mean oral clearance and volume of distribution averaged 0,21 ± 0,08 l/h/kg and 2,4 ± 0,8 l/kg while $t_{1/2}$ averaged 8,7 ± 3,5 hrs in heart transplant patients.

Metabolism and biotransformation

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

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present al low concentrations. Therefore, metabolites do not contribute to the pharmacological activity of tacrolimus.

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. Children require a higher dose of tacrolimus; approximately 1½ to 2 times higher than that recommended for adults, possibly owing to a higher metabolic turnover.

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

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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

Carcinogenesis

Carcinogenicity studies in male and female rats and mice showed no relationship of tumour incidence to tacrolimus dosage was found. (see Boxed Warning and section 4.4).

Mutagenesis

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Impairment of fertility

Tacrolimus administered orally to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryo-lethality and adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryo-lethal effects were indicated by a higher rate of pre- and post-implantation loss and increased numbers of undelivered and nonviable pups. When administered at 2,6 to 6,9 times the clinical dose range based on body surface area, tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on oestrus cycles, parturition, pup viability, and pup malformations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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Capsule fill:

Croscarmellose sodium

Hypromellose 2910

Lactose monohydrate

Magnesium stearate (E572)

Capsule shell:

The 0,5 mg capsule shell contains, FD & C Blue 1 (E133), FD & C Red 40 (E129), gelatin and titanium dioxide (E171).

The 1 mg capsule shell contains FD & C Blue 1 (E133), gelatin, iron oxide yellow (E172) and titanium dioxide (E171).

The 5 mg capsule shell contains D & C Red 28, D & C Yellow 10 (E104), FD & C Blue 1, gelatin, and titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

HDPE Bottles: 36 months.

PVC/ PVDC Aluminium blister pack: 18 months

6.4 Special precautions for storage

Store at or below 25 °C. Store in the original package until required for use.

HDPE Bottles: Keep the bottle tightly closed.

Blisters: Do not remove blisters from carton until required for use.

6.5 Nature and contents of container

HDPE container: 100 capsules packed in a transparent, round 50 ml HDPE container closed with a white, opaque plastic cap.

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Blister pack: 10 capsules packed in aluminium foil (PVC/PVDC) blisters. 10 of such blisters will be packed in a printed carton.

Pack size: 100 capsules.

6.6 Special precautions for disposal and other handling

No specific precautions applicable.

7 HOLDER OF CERTIFICATE OF REGISTRATION

STRIDES PHARMA SA (PTY) LTD

106 16th Road

Building 2

Midrand

South Africa

1685

8 REGISTRATION NUMBERS

GRAFOLIN 0,5 mg: 540814.811

GRAFOLIN 1 mg: 540815.812

GRAFOLIN 5 mg: 540816.813

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date on the registration certificate of the medicine.

10 DATE OF REVISION OF THE TEXT

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