NAME OF THE MEDICINAL PRODUCT
SALVADO® 0.5 (Tacrolimus capsules USP 0.5mg)
SALVADO® 1 (Tacrolimus capsules USP 1mg)
SALVADO® 5 (Tacrolimus capsules USP 5mg)

DESCRIPTION AND COMPOSITION

Description:

Hard gelatin capsules with light yellow opaque body and light yellow opaque cap imprinted with (Biocon's logo) on the cap and "T 0.5" on the body with red ink.

Hard Gelatin capsules with white opaque body and white opaque cap imprinted with "" (Biocon's logo) on the cap and "T 1" on the body with red ink.

Hard Gelatin capsules with a greyish red opaque body and greyish red opaque cap imprinted with "" (Biocon's logo) on the cap and "T 5" on the body with white ink.

Composition:

Active ingredient
Hard gelatin capsules containing 0.5mg, 1mg and 5mg Tacrolimus.

Excipients
Excipient with knowneffect: Lactose anhydrous.
Other excipients of capsule content: Hypromellose, Croscarmellose sodium, Magnesium stearate.

Composition of empty hard gelatin capsules
- 0.5 mg capsule shell contains Iron oxide yellow (E172), Titanium dioxide (E171) & Gelatin
- 1 mg capsule shell contains Titanium dioxide (E171) & Gelatin
- 5 mg capsule shell contains Iron oxide red (E172), Titanium dioxide (E171) & Gelatin

Printing ink of capsule shell
- 0.5 mg & 1 mg: Shellac (E904), Propylene glycol (E1520), Sodium hydroxide (E524), Titanium dioxide (E171), Povidone (E1201) & FD&C Red aluminium lake (E129)
- 5 mg: Shellac (E904), Propylene glycol (E1520), Ammonia solution (E527), Potassium hydroxide (E525) & Titanium dioxide (E171)

THERAPEUTIC INDICATION
Primary immunosuppression in liver and kidney allograft recipients and liver and kidney allograft rejection resistant to conventional immunosuppressive agents.

POSOLOGY AND METHOD OF ADMINISTRATION
Only physicians experienced in immunosuppressive therapy and the management of organ transplant patients should prescribe tacrolimus. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resourced. The physician responsible for maintenance therapy should have complete information requisite for the follow up of the patient.

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

Dosing should commence orally, if necessary via an intranasal gastric tube. If the clinical

condition of the patient does not allow oral therapy, initial intravenous dosing may be necessary.

Dosage recommendations

Primary Immunosuppression Dose Levels – Adults
Liver and kidney transplantation: Oral tacrolimus therapy should commence at 0.10 – 0.20 mg/kg/day for liver transplantation and at 0.15 – 0.30 mg/kg/day for kidney transplantation administered as two divided doses. Administration should start approximately 6 hours after the completion of liver transplant surgery and within 24 hours after completion of kidney transplant surgery. If clinical condition of the patient does not allow oral dosing, then intravenous tacrolimus therapy should be initiated as a continuous 24 hours infusion at 0.01 to 0.05 mg/kg for liver transplant and 0.05 to 0.10 mg/kg for kidney transplant.

Primary Immunosuppression Dose Levels – Paediatric Patients
Paediatric patients generally require doses 1.5 to 2 times higher than the recommended adult doses to achieve the same blood levels.

Liver and kidney transplantation: An initial dose of 0.3 mg/kg/day for liver and kidney transplantation should be administered in two divided doses. If the dose cannot be given orally, an initial intravenous dose of 0.05 mg/kg/day for the liver transplantation or 0.1 mg/kg/day for kidney transplantation should be administered as a continuous 24 hour infusion.

Maintenance Therapy Dose Levels
It is necessary to continue immunosuppression with oral tacrolimus to maintain graft survival. Dose can frequently be reduced during maintenance therapy. Dosing should be primarily based on clinical assessments of rejection and tolerability of the patient.

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

If signs of toxicity (e.g. pronounced adverse event) are noted, the dose of tacrolimus should be reduced.

When tacrolimus is administered in combination with a corticosteroid these may often be reduced and in rare cases the treatment has continued as monotherapy.

Therapy Dose Levels for Liver and Kidney Allograft Rejection Resistant to Conventional Immunosuppressive Regimens
In patients experiencing rejections episodes which are unresponsive to conventional immunosuppressive therapy, tacrolimus treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.
Tacrolimus should be initiated after considering cyclosporin blood concentrations and the clinical condition of the patient. In practice, tacrolimus therapy has been initiated 12-24 hours after discontinuation of cyclosporin. Monitoring of cyclosporin blood levels should be continued following conversion as the clearance of cyclosporin may be affected.

Duration of dosing
For oral dosing the capsules normally have to be taken continuously to suppress graft rejection and no limit for therapy duration can be given. Patients should be converted from intravenous to oral medication as soon as individual circumstances permit. Intravenous

therapy should not be continued for more than 7 days.

Mode of Intake
Capsules 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 (See Pharmacokinetic properties).

Monitoring of Whole Blood Concentrations
Drug level monitoring is recommended during the early post-transplantation period, following dose adjustment of tacrolimus therapy after switching from another immunosuppressive regimen or following co-administration of drugs which are likely to lead to a drug interaction. Trough blood levels of tacrolimus should also be monitored periodically during maintenance therapy. The frequency of blood level monitoring should be based on clinical needs. As tacrolimus has a long half-life, it can take several days for adjustments in tacrolimus dosing to be reflected in changes in blood levels.

Patient with Liver Impairment
A dose reduction is necessary.

Patient with Renal Impairment
Careful monitoring of renal function including serial creatinine estimations, calculations of creatinine clearance and monitoring urine output is recommended.

Elderly Patients
There is no evidence currently available to indicate that dosing should be adjusted in older people.

CONTRAINDICATIONS
- Known hypersensitivity to tacrolimus or other macrolides.
- Tacrolimus Capsules 1mg and Tacrolimus Capsules 5mg in addition; Known hypersensitivity to other ingredients

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
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; alterationsin formulation or regimen should only take place under the close supervision of a transplant specialist.

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.

<u>Substances with potential for interaction</u>
When substances with a potential for interaction (see section Interactions with other medicinal products and other forms of interaction) - particularly strong inhibitors of CYP3A4 (such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers of CYP3A4 (such as rifampicin, rifabutin) – are being combined with tacrolimus, tacrolimus blood levels should 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) or other herbal preparations should be avoided when taking Tacrolimus due to the risk of interactions that lead to decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus (see section Interactions with other medicinal products and other forms of interaction).

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 Posology and method of administration and Interaction with other medicinal products and other forms of interaction).

High potassium intake or potassium-sparing diuretics should be avoided (see section Interaction with other medicinal products and other forms of interaction).

Certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see Interaction with other medicinal products and other forms of interaction.

Vaccination
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.

Gastrointestinal disorders
Gastrointestinal perforation has been reported in patients treated with tacrolimus. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments should be considered immediately after suspected symptoms or signs occur.

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 on rare occasions. Most cases have been reversible, occurring primarily in children 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, particularly young children and those receiving substantial 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 Tacrolimus therapy, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval and may cause Torsades de Pointes.
Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, bradyarrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure (see section Interaction with other medicinal products and other forms of interaction).

Lymphoproliferative disorders and malignancies

Patients treated with Tacrolimus have been reported to develop Epstein-Barr virus (EBV)-associated lymphoproliferative disorders (see section Undesirable effects).
Patients switched to Tacrolimus therapy should not receive anti-lymphocyte treatment concomitantly. Very young (<2 years old), EBV-VCA-negative children have been reported to be have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with Tacrolimus. 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 immunosuppressive agents, owing to the potential risk of malignant skin changes, exposures to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section Undesirable effects).

Posterior reversible encephalopathy syndrome (PRES)
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 control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Opportunistic infections
Patients treated with immunosuppressants, including tacrolimus 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 patients with deteriorating hepatic or renal function or neurological symptoms.

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.

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

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Metabolic interactions
Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels.
It is therefore strongly recommended to closely monitor tacrolimus blood levels, as well as, QT prolongation (with ECG), renal function and other side effects, whenever substances which

have the potential to alter CYP3A4 metabolism are used concomitantly and to interruptor adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections posology and method of administration & Special warnings and precautions for use).

Inhibitors of metabolism

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 antibiotics erythromycin, HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g. telaprevir, boceprevir) and CMV antiviral letermovir. Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients.

Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, amiodarone, danazol, ethinylestradiol, omeprazole, nefazodone and herbal remedies containing extracts of Schisandra sphenanthera.

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, norethisterone, quinidine, tamoxifen, troleandomycin.

Naringenine (flavonoid in 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 medicinal products known to have a high affinity for plasma proteins should be considered (e.g. NSAIDs, oral anticoagulants, oral antidiabetics).
Other potential interactions that may increase systemic exposure of tacrolimus include the prokinetic agent metoclopramide, cimetidine and magnesium-aluminium-hydroxide.

Inducers of metabolism

Clinically the following substances have been shown to decrease tacrolimus blood levels: Strong interactions have been observed with rifampicin, phenytoin or 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.

Tacrolimus should not be administered concurrently with ciclosporin. 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 (see sections posology and method of administration & Special warnings and precautions for use).

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. Available data suggests 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 phenazone.

Other interactions which have led to clinically detrimental effects
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase toxic effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole+ trimethoprim, 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, triameterine, or spironolactone) should be avoided (see section special warnings and precautions for use).

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

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Human data show that tacrolimus is able to cross the placenta and infants exposed to tacrolimus *in utero* may be at a risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress.

The use of tacrolimus during pregnancy has been associated with preterm delivery, neonatal hyperkalemia and renal dysfunction.

Tacrolimus may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly.

Tacrolimus may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure.

Females and males of reproductive potential should consider the use of appropriate contraception prior to starting treatment of tacrolimus.

Due to the need of treatment, tacrolimus 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 rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity.

Breast-feeding

Human data demonstrate that tacrolimus is excreted into breast milk. The effects of tacrolimus on the breastfed infant, or on milk production have not been assessed. As detrimental effects on the new born cannot be excluded, women should not breast feed whilstreceiving tacrolimus.

Fertility

A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats (see section preclinical safety data).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if tacrolimus is administered in association with alcohol.

UNDESIRABLE EFFECTS

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

Many of the adverse drug reactions stated below are reversible and/or respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse events compared with intravenous use. Adverse drug reactions 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); not known (cannot be estimated from the available data).

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 tacrolimus.

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 EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Blood and lymphatic system disorders

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

Immune system disorders

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section special warnings and precautions for use).

Endocrine disorders

rare:	Hirsutism

Metabolism and nutrition disorders

very common:	hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common:	hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, 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, writing impaired, 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:	vision blurred, photophobia, eye disorders
uncommon:	cataract
rare:	blindness
not known:	optic neuropathy

Ear and labyrinth disorders

common:	tinnitus uncommon: hypoacusis
rare:	deafness neurosensory
very rare:	hearing impaired

Cardiac disorders

common:	ischaemic coronary artery disorders, tachycardia
uncommon:	ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal
rare:	pericardial effusion
very rare:	echocardiogram abnormal, electrocardiogram QT prolonged, *Torsades de Pointes*

Vascular disorders

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

Respiratory, thoracic and mediastinal disorders

common:	dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations
uncommon:	respiratory failures, 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:	ileus paralytic, acute and chronic pancreatitis, amylase increased, gastrooesophageal reflux disease, impaired gastric emptying
rare:	subileus, pancreatic pseudocyst

Hepatobiliary disorders

common:	hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
rare:	hepatitic artery thrombosis, venoocclusive liver disease
very rare:	hepatic failure, bile duct stenosis

Skin and subcutaneous tissue disorders

common:	pruritus, rash, alopecia, 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, muscle spasms, pain in extremity, back pain
uncommon:	joint disorders
rare:	mobility decrease

Renal and urinary disorders

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

Reproductive system and breast disorders

uncommon:	dysmenorrhoea and uterine bleeding

General disorders and administration site conditions

common:	asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed
uncommon:	multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased
rare:	thirst, fall, chest tightness, ulcer very rare: fat tissue increased
not known:	febrile neutropenia

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).

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

OVERDOSE
Experience with overdosage is limited. Several cases of accidental overdosage have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy, increased blood urea nitrogen and elevated serum creatinine concentrations and increase in alanine aminotransferase levels.

No specific antidote to tacrolimus therapy is available. If overdosage 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 and diafiltration have been effective in reducing toxic concentrations. In cases of oral intoxication, gastric lavage and/or the use of absorbents (such as activated charcoal) may be helpful, if used shortly after intake.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Calcineurin inhibitors, ATC code: L04AD02

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 lymphokine genes.

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

In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes which are mainly responsible for graft rejection. The drug suppresses T-cell activation and T-helper cell dependant B-cell proliferation as well as the formation of lymphokines such as interleukins-2, -3 and gamma interferon and the expression of the interleukin-2 receptor.

Pharmacokinetic properties

Absorption

In man, tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Following oral administration of tacrolimus capsules, peak concentrations (C_{max}) of the tacrolimus in blood are achieved in approximately 1 to 3 hours. In some patients the drug appears to be continuously absorbed over a prolonged time period yielding more or less a flat absorption profile. The mean oral bioavailability of tacrolimus is in the range of 20% - 25%.

After oral administration (0.30mg/kg/day) to liver transplant patients, steady state concentrations of tacrolimus were achieved within 3 days in most patients.

In healthy subjects, tacrolimus 0.5 mg, tacrolimus 1 mg and tacrolimus 5 mg Capsules have been shown to be bioequivalent, when administered as equivalent dose.

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases both the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.

In stable liver transplant patients, the oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat (34% of calories) content. Decreases in AUC (27%) and C_{max} (50%), and an increase in t_{max} (173%) in whole blood were evident.

In a study of stable renal transplant patients who were administered tacrolimus immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced.

Decreases in AUC (2 to 12%) and C_{max} (15 to 38%), and an increase in t_{max} (38 to 80%) in whole blood were evident.

Bile flow does not influence the absorption of tacrolimus and therefore commencement of tacrolimus therapy with an oral dose or early conversion of liver transplant patients from intravenous to oral therapy is possible. There is strong correlation between the area under the curve (AUC) and the whole blood trough levels at steady state. Thus monitoring of whole blood trough levels provides a good estimate of systemic exposure.

Distribution and elimination

In man the disposition of tacrolimus after intravenous infusions may be describes as biphasic. In systemic circulation, tacrolimus binds strongly to erythrocytes resulting in the distribution of whole blood/plasma concentrations of tacrolimus is approximately 20:1. In plasma the drugis highly plasma 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 1300L (healthy subjects). Corresponding data based on whole blood data averaged 47.6L.

The total body clearance (TBC) of tacrolimus from blood is low. In healthy subjects the average TBC estimated from whole blood concentrations was 2.25L/h. In adult liver and kidney transplant patients, values of 4.1L/h and 6.7L/h respectively, have been observed. In paediatric liver transplant patients, the TBC is approximately twice that of adult liver transplant patients.

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.

There is evidence that pharmacokinetics of tacrolimus change with improving clinical conditions of the patients. In liver transplant patients, the mean oral dose was decreased by 28% from day 7 to month 6 after transplantation to maintain similar mean trough levels of tacrolimus. Change in clearance and/or bioavailability were suggested as probable causes for this effect.

The half-life of tacrolimus is long and variable. In healthy volunteers the main half-life in whole blood is approximately 43 hours. In paediatric and adult liver transplant patients, it averaged 12.4 hours and 11.7 hours respectively. In adult kidney transplant patients, it averaged 15.6 hours.

Increased clearance rates contribute to the shorter half-life observed in transplant recipients.

Metabolism and biotransformation

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 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 the faeces. This indicates that tacrolimus is almost completely metabolized prior to elimination from the body and that the bile is the principal route of elimination.

Clinical Studies in Patients with Lupus Nephritis

Patients with lupus nephritis who were refractory to steroid monotherapy and exhibited clinical signs of chronic nephritis with immunological activity were treated with tacrolimus capsules (a dose of 3mg, once daily after supper) for 28 weeks in the Phase III trial. The rate of change in the total score* of disease activity at the final measurement was –32.9%. The rate of change in the actual values of daily urinary protein excretion and complement (C3), which are indices of chronic nephritis and immunological activity, respectively, were –60.8%and 16.4%, and the change in creatinine clearance (CCr) was –22.0%.

	Tacrolimus group [n=27]	Placebo group [n=34]	95% confidence intervals for the differences between groups
The rate of change in the total score of disease activity* (%), mean ± S.D.	–32.9 ± 31.0	2.3 ± 38.2	−
The rate of change in the actual value of daily urinary protein excretion (%), median (1st quartile, 3rd quartile)	–60.8 (–73.7, –37.2)	8.7 (–14.0, 90.0)	[–115.0 to –48.7]
The rate of change in the actual value of complement (C3) (%), median (1st quartile, 3rd quartile)	16.4 (10.3, 27.5)	–2.8 (–11.1, 18.2)	[8.5 to 26.7]
The rate of change in the actual value of CCr (%), median (1st quartile, 3rd quartile)	–22.0** (–33.5, –4.2)	–1.4 (–19.3, 16.9)	[–30.5 to –3.4]

*Total score of disease activity consists of the sum of the scores (a 4-point scale, ranging from 0 to 3 per item) of 5 items: daily urinary protein excretion, urinary red blood cells, serum creatinine, anti-ds DNA antibody, and complement (C3).
** As for the evaluation of CCr only, the number of cases for the tacrolimus group was 26.

The major adverse reactions or abnormalities in clinical laboratory findings due to tacrolimus capsules in 65 patients with lupus nephritis in Phase II and Phase III trials were β2 microglobulin urine increased (27.3%, 12/44), urinary NAG increased (22.2%, 14/63), nasopharyngitis (15.4%, 10/65), hyperuricaemia (14.1%, 9/64), leukocytosis (14.1%, 9/64), creatinine increased (12.5%, 8/64), diarrhoea (12.3%, 8/65), blood pressure increased (10.8%, 7/65), and hyperglycaemia (10.9%, 7/64).

Preclinical Safety Data
Embryotoxicity was observed in animal studies.

Tacrolimus subcutaneously administered to male rats at a doses of 2 or 3 mg/kg/day (1.6 to 6.4 times the clinical dose range based on body surface area) resulted in a dose-related decrease in sperm count.

Tacrolimus given orally at 1.0 mg/kg (0.8 to 2.2 times the clinical dose range based on body surface area) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and adverse effects on female reproduction which were indicated by a higher rate of post-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (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 estrus cycles, parturition, pup viability, and pup malformations.

PHARMACEUTICAL PARTICULARS

Incompatibilities
Tacrolimus is unstable under alkaline conditions.

PRESENTATION
Pack size:
100 Capsules (10 × 10s): 10 capsules are packed in a blister comprising of Alu-Alu blister. 10 such blisters are placed in an outer carton.
50 Capsules (5 × 10s): 10 capsules are packed in a blister comprising of Alu-Alu blister. 5 such blisters are placed in an outer carton.
Note: Not all pack sizes may be marketed.

SHELF LIFE
24 months

SPECIAL PRECAUTIONS FOR STORAGE
Salvado® (Tacrolimus Capsules USP 0.5mg, 1mg and 5mg)
Store at or below 30˚C.
Protect from moisture.

INSTRUCTIONS FOR USE/HANDLING
Tacrolimus Capsules should be taken immediately following removal from the blister.

PRODUCT REGISTRANT
DKSH Singapore Pte Ltd
47 Jalan Buroh #09-01
Singapore 619491

Manufactured by:
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