SUMMARY OF PRODUCT CHARACETRISTICS

1 NAME OF THE MEDICAL PRODUCT

Vingraf 1 mg / 5 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vingraf 1 mg Capsules
Each hard gelatin capsule contains tacrolimus 1 mg

Vingraf 5 mg Capsules
Each hard gelatin capsule contains tacrolimus 5 mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis of Organ Rejection in Kidney, Liver, and Heart Transplant
Vingraf is indicated for the prophylaxis of organ rejection, in adult and pediatric patients receiving allogeneic kidney transplant, liver transplants and heart transplant, in combination with other immunosuppressants.

4.2 Posology and method of administration

Vingraf should not be used without supervision by a physician with experience in immunosuppressive therapy.

Posology

If patients are able to tolerate oral therapy, the recommended oral starting doses should be initiated. The initial dose of Vingraf capsules should be administered no sooner than 6 hours after transplantation in the liver and heart transplant patients. In kidney transplant patients, the initial dose of Vingraf capsules may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered. Adults

The initial oral Vingraf capsule dosage recommendations for adult patients with kidney, liver, or heart transplants and whole blood trough concentration range are shown in Table 1. Perform therapeutic drug monitoring (TDM) to ensure that patients are within the ranges listed in Table 1.

Table 1. Summary of Initial Oral Vingraf Capsules Dosing Recommendations and Whole Blood Trough

Concentration Range in Adults

Patient Population	**Tacrolimus Capsules* Initial Oral Dosing**	**Whole Blood Trough Concentration Range**
Kidney Transplant		
With Azathiprione	0.2 mg/kg/day, divided in two doses, administered every 12 hours	Month 1-3: 7-20 ng/mL Month 4-12: 5-15 ng/mL
With MMF/IL-2 receptor antagonist†	0.1 mg/kg/day, divided in two doses, administered every 12 hours	Month 1-12: 4-11 ng/mL
Liver Transplant		
With corticosteroids only	0.10-0.15 mg/kg/day, divided in two doses, administered every 12 hours	Month 1-12: 5-20 ng/mL
Heart Transplant		
With azathioprine or MMF	0.075 mg/kg/day, divided in two doses, administered every 12 hours	Month 1-3: 10-20 ng/mL Month ≥ 4: 5-15 ng/mL

*African-American patients may require higher doses compared to Caucasians (see Table 2).

† In a second smaller trial, the initial dose of tacrolimus was 0.15-0.2 mg/kg/day and observed tacrolimus concentrations were 6-16 ng/mL during month 1-3 and 5-12 ng/mL during month 4-12.

Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower Vingraf dosages than the recommended initial dosage may be sufficient as maintenance therapy. Adjunct therapy with adrenal corticosteroids is recommended early post-transplant.

The data in kidney transplant patients indicate that the African-American patients required a higher dose to attain comparable trough concentrations compared to Caucasian patients (Table 2) Table 2. Comparative Dose and Trough Concentrations Based on Race

Time after transplant	Caucasian (n=114)	African-American (n=56)

	Dose (mg/kg)	Trough Concentrations (ng/mL)	Dose (mg/kg)	Trough Concentrations (ng/mL)
Day 7	0.18	12.0	0.23	10.9
Month 1	0.17	12.8	0.26	12.9
Month 6	0.14	11.8	0.24	11.5
Month 12	0.13	10.1	0.19	11.0

Children

Pediatric patients in general need higher tacrolimus doses compared to adults: the higher dose requirements may decrease as the child grows older. Recommendations for the initial oral dosing for pediatric transplant patients and whole blood trough concentration range are shown in Table 3. Perform TDM to ensure that patients are within the ranges listed in Table 3.

Table 3. Summary of Initial tacrolimus capsule dosing recommendations and Whole Blood Trough
Concentration Range in Children

Patient population	**Initial Tacrolimus Capsule**	**Whole Blood Trough Concentration Range**
Pediatric kidney transplant patients	0.3 mg/kg/day capsules divided in two doses, administered every 12 hours	Month 1-12: 5-20 ng/mL
Pediatric liver transplant patients	0.15-0.2 mg/kg/day capsules divided in two doses, administered every 12 hours	Month 1-12: 5-20 ng/mL
Pediatric heart transplant patients	0.3 mg/kg/day* capsules divided in two doses, administered every 12 hours	Month 1-12: 5-20 ng/mL

* 0.1 mg/kg/day if cell depleting induction treatment is administered

For conversion of pediatric patients from any other formulation of tacrolimus capsules, the total daily dose should remain the same. Following conversion from one formulation to another formulation of tacrolimus, therapeutic drug monitoring is recommended.

Special population

Renal impairment

Due to its potential for nephrotoxicity, consideration should be given to dosing tacrolimus at the lower end of the therapeutic dosing range in patients who have received a liver or heart transplant and have preexisting renal impairment. Further reductions in dose below the targeted range may be required. In kidney transplant patients with post-operative oliguria, the initial dose of tacrolimus should be administered no sooner than 6 hours and within 24 hours of transplantation, but may be delayed until renal function shows evidence of recovery.

Hepatic impairment

Due to the reduced clearance and prolonged half-life, patients with severe hepatic impairment (Child-Pugh ≥ 10) may require lower doses of tacrolimus. Close monitoring of blood concentrations is warranted.

The use of tacrolimus in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole blood concentrations of tacrolimus. These patients should be monitored closely and dosage adjustments should be considered.

Some evidence suggests that lower doses should be used in these patients.

Therapeutic Drug Monitoring

Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments, and compliance. Whole blood trough concentration range can be found in Table 1.

Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting drugs and the post-transplant time. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies. Data from clinical trials show that tacrolimus whole blood concentrations were most variable during the first week post-transplantation.

The relative risks of toxicity and efficacy failure are related to tacrolimus whole blood trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity and efficacy failure.

Method of administration

Under- or overexposure to tacrolimus may result in graft rejection or other serious adverse reactions. Changes between tacrolimus immediate-release and extended-release dosage forms must occur under physician supervision.

The recommended starting doses should be initiated in oral therapy. Tacrolimus capsules may be taken with or without food. However, since the presence of food affects the bioavailability of tacrolimus, if taken with food, it should be taken consistently the same way each time.

General Administration Instructions

Patients should not eat grapefruit or drink grapefruit juice in combination with tacrolimus.

Tacrolimus should not be used simultaneously with cyclosporine. Tacrolimus or cyclosporine should be discontinued at least 24 hours before initiating the other.

In the presence of elevated tacrolimus or cyclosporine concentrations, dosing with the other drug usually should be further delayed. Therapeutic drug monitoring (TDM) is recommended for all patients receiving tacrolimus.

4.3 Contraindications

- Hypersensitivity to tacrolimus or to any of the excipients listed in section 6.1. Hypersensitivity symptoms reported include dyspnea, rash, pruritus and acute respiratory distress syndrome.

4.4 Special warnings and precautions for use

Lymphoma and Other Malignancies

Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

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:

- Polyomavirus-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

Not Interchangeable with Extended-Release Tacrolimus Products - Medication Errors

Medication errors, including substitution and dispensing errors, between tacrolimus immediaterelease 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. 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 and to confirm with the healthcare provider if a different product is dispensed.

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. Blood glucose concentrations should be monitored closely in patients using tacrolimus.

Nephrotoxicity

Tacrolimus, like other calcineurin inhibitors, can cause acute or chronic nephrotoxicity. Nephrotoxicity was reported in clinical trials. 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 drugs associated with nephrotoxicity (e.g., aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors, protease inhibitors). 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, paresthesias, headache, mental status changes, and changes in motor and sensory functions. 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 tacrolimus if neurotoxicity occurs.

Hyperkalemia

Hyperkalemia has been reported with tacrolimus use. Serum potassium levels should be monitored. Careful consideration should be given prior to use of other agents also associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) during tacrolimus therapy. Monitor serum potassium levels periodically during treatment.

Hypertension

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

Not recommended for use with Sirolimus

Tacrolimus 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 in a U.S. trial 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 are recommended.

QT prolongation

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, bradyarrhythmias, those taking certain antiarrhythmic medications or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia, 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.

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 tacrolimus should be considered.

Immunizations

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

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 tacrolimus should be considered.

4.5 Interaction with other medicinal products and other forms of Interaction

Mycophenolic acid

When tacrolimus is prescribed with a given dose of a mycophenolic acid (MPA) product, exposure to MPA is higher with tacrolimus co-administration than with cyclosporine co-administration with MPA, because cyclosporine 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 products as needed. * Tacrolimus dosage adjustment recommendation based on observed effect of coadministered drug on tacrolimus exposures, literature reports of altered tacrolimus exposures, or the other drug's known CYP3A inhibitor/inducer status.

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Effects of other drugs on tacrolimus

Drug/Substance Class or Name	**Drug 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)	Avoid grapefruit or grapefruit juice.
Strong CYP3A Inducers‡: Antimycobacterials (e.g rifampin, rifabutin), anticonvulsants (e.g. phenytoin, carbamazepine and phenobarbital), St. John's wort	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection	Increase tacrolimus dose and monitor tacrolimus whole blood trough concentrations

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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), nefazodone, letermovir, Schisandra sphenanthera extracts	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation)	Reduce tacrolimus dose (for voriconazole and posaconazole, give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations
Mild or Moderate CYP3A Inhibitors: Clotrimazole, antibiotics (e.g., erythromycin, fluconazole), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl estradiol, cimetidine, lansoprazole and omeprazole	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation)	Monitor tacrolimus whole blood trough concentrations and reduce Vingraf dose if needed
Other drugs, such as: Magnesium and aluminum hydroxide antacids Metoclopramide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation)	Monitor tacrolimus whole blood trough concentrations and reduce Vingraf dose if needed
Mild or moderate CYP3A inducers Methylprednisolone, prednisone	May decrease tacrolimus concentrations.	Monitor tacrolimus whole blood trough concentrations and adjust Vingraf dose if needed

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

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*** 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 drug-drug interaction studies with midazolam (sensitive CYP3A probe substrate).

4.6 Pregnancy and Lactation

Pregnancy:

Tacrolimus can cause fetal harm when administered to a pregnant woman. Data from postmarketing surveillance suggest that infants exposed to tacrolimus *in utero* are at a risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress. Advise pregnant women of the potential risk to the fetus.

The background risk of major birth defects and miscarriage in the indicated population is unknown. *Women of childbearing potential*

Tacrolimus can cause fetal harm when administered to pregnant women. Advise female and male patients of reproductive potential to speak to their healthcare provider on family planning options including appropriate contraception prior to starting treatment with this medicine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Risks during pregnancy are increased in organ transplant recipients.

The risk of premature delivery following transplantation is increased. Pre-existing hypertension and diabetes confer additional risk to the pregnancy of an organ transplant recipient. Pre-gestational and gestational diabetes are associated with birth defects/congenital anomalies, hypertension, low birth weight and fetal death.

Cholestasis of pregnancy (COP) was reported in 7% of liver or liver-kidney (LK) transplant recipients, compared with approximately 1% of pregnancies in the general population. However, COP symptoms resolved postpartum and no longterm effects on the offspring were reported.

Maternal Adverse Reactions

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.

Fetal/Neonatal Adverse Reactions

Renal dysfunction, transient neonatal hyperkalemia and low birth weight have been reported at the time of delivery in infants of mothers taking tacrolimus.

Labor or Delivery

There is an increased risk for premature delivery (< 37 weeks) following transplantation and maternal exposure to tacrolimus.

There are no adequate and well controlled studies on the effects of tacrolimus in human pregnancy. Safety data from the postmarketing surveillance suggest infants exposed to tacrolimus *in utero* have an increased risk for miscarriage, pre-term delivery (< 37 weeks), low birth weight (< 2500 g), birth defects/congenital anomalies and fetal distress.

Breast-feeding

Controlled lactation studies have not been conducted in humans; however, tacrolimus has been reported to be present in human milk. The effects of tacrolimus on the breastfed infant, or on milk production have not been assessed. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tacrolimus and any potential adverse effects on the breastfed child from tacrolimus or from the underlying maternal condition.

Fertility

Based on findings in animals, male and female fertility may be compromised by treatment with tacrolimus.

4.7 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.

4.8 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 drug reactions 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. **System organ class**	**Frequency**	**Adverse reactions**

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
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

	Very common	insomnia
Psychiatric disorders	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	Visual blurred, photophobia, eye disorders
	Uncommon	Cataract
	Rare	blindness
	Not known	Optic neuropathy
Ear and labyrinth disorders	Common	Tinnitus
	Uncommon	Hypoacusis
	Rare	Blindness
	Not known	Optic neuropathy
Cardiac disorders	Common	ischaemic coronary artery disorders, tachycardia
	Uncommon	ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations
	Rare	pericardial effusion
	Very rare	*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, gastrooesophageal reflux disease, impaired gastric emptying
	Rare	subileus, pancreatic pseudocyst
Hepatobiliary disorders	Common	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, alopecias, acne, sweating increased
	Uncommon	dermatitis, photosensitivity
	Rare	Toxic epidermal necrolysis (Lyell's syndrome)
	Very rare	Stevens Johnson syndrome
Musculoskeletal and connective tissue disorders	Common	Arthralgia, muscle spasms, pain in extremity, back pain
	Uncommon	Joint disorders
	Rare	Mobility decreased
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, body temperature perception disturbed
	Uncommon	multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal,
	Rare	thirst, fall, chest tightness, ulcer
	Very rare	fat tissue increased
	not known	febrile neutropenia
Investigations	Common	hepatic enzymes and function abnormalities, blood alkaline phosphatase increased, weight increased
	Uncommon	amylase increased, ECG investigations abnormal, heart rate and pulse investigations abnormal, weight decreased, blood lactate dehydrogenase increased
	Very rare	echocardiogram abnormal, electrocardiogram QT prolonged
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).

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

Reporting of suspected adverse reactions:
Healthcare professionals are requested to report any suspected adverse reactions via the national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities.

4.9 Overdose

Limited overdosage experience is available. Acute overdosages of up to 30 times the intended dose have been reported. Almost all cases have been asymptomatic and all patients recovered with no sequelae. Acute overdosage was sometimes followed by adverse reactions consistent with those listed in Adverse Reactions (6) (including tremors, abnormal renal function, hypertension, and peripheral edema); in one case of acute overdosage, transient urticaria and lethargy were observed. Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

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

Mechanism of action

Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (a ubiquitous mammalian intracellular enzyme) is then formed, after which the phosphatase activity of calcineurin is inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT), and nuclear factor kappa-light-chain enhancer of activated B-cells (NF-κB).

Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colonystimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming

growth factor beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation, as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

Clinical studies

Kidney transplantation

Tacrolimus/Azathioprine (AZA)

Tacrolimus based immunosuppression in conjunction with azathioprine and corticosteroids following kidney transplantation was assessed in a randomized, multicenter, non-blinded, prospective trial. There were 412 kidney transplant patients enrolled at 19 clinical sites in the United States. Study therapy was initiated when renal function was stable as indicated by a serum creatinine ≤ 4 mg/dL (median of 4 days after transplantation, range 1 to 14 days). Patients less than 6 years of age were excluded.

There were 205 patients randomized to tacrolimus-based immunosuppression and 207 patients were randomized to cyclosporine-based immunosuppression. All patients received prophylactic induction therapy consisting of an antilymphocyte antibody preparation, corticosteroids, and azathioprine. Overall 1-year patient and graft survival was 96.1% and 89.6%, respectively.

Data from this trial of tacrolimus in conjunction with azathioprine indicate that during the first 3 months of that trial, 80% of the patients maintained trough concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through 1 year.

Tacrolimus/Mycophenolate mofetil (MMF)

Tacrolimus-based immunosuppression in conjunction with MMF, corticosteroids, and induction has been studied. In a randomized, open-label, multicenter trial (Study 1), 1589 kidney transplant patients received tacrolimus (Group C, n = 401), sirolimus (Group D, n = 399), or one of two cyclosporine (CsA) regimens (Group A, n = 390 and Group B, n = 399) in combination with MMF and corticosteroids; all patients, except those in one of the two cyclosporine groups, also received induction with daclizumab. The trial

was conducted outside the United States; the trial population was 93% Caucasian. In this trial, mortality at 12 months in patients receiving tacrolimus/MMF was similar (3%) compared to patients receiving cyclosporine/MMF (3% and 2%) or sirolimus/MMF (3%). Patients in the tacrolimus group exhibited higher estimated creatinine clearance rates (eCLcr) using the Cockcroft-Gault formula and experienced fewer efficacy failures, defined as biopsy-proven acute rejection (BPAR), graft loss, death, and/or loss to follow-up in comparison to each of the other three groups. Patients randomized to tacrolimus/MMF were more likely to develop diarrhea and diabetes after the transplantation and experienced similar rates of infections compared to patients randomized to either cyclosporine/MMF regimen.

Table: Estimated Creatinine Clearance at 12 Months (Study 1)

Group	eCL_{cr} [mL/min] at Month 12*				
	N	**MEAN**	**SD**	**MEDIAN**	**Treatment Difference with Group C (99.2% CI†)**
(A) CsA/MMF/CS	390	56.5	25.8	56.9	-8.6 (-13.7, -3.7)
(B) CsA/MMF/CS/Daclizumab	399	58.9	25.6	60.9	-6.2 (-11.2, -1.2)
(C) Tac/MMF/CS/Daclizumab	401	65.1	27.4	66.2	-
(D) Siro/MMF/CS/Daclizumab	399	56.2	27.4	27.3	-8.9 (-14.1, -3.9)
Total	1589	59.2	26.8	60.5	

Key: CsA = Cyclosporine, CS = Corticosteroids, Tac = Tacrolimus, Siro = Sirolimus

* All death/graft loss (n = 41, 27, 23, and 42 in Groups A, B, C, and D) and patients whose last recorded creatinine values were prior to month 3 visit (n = 10, 9, 7, and 9 in Groups A, B, C, and D, respectively) were imputed with Glomerular Filtration Rate (GFR) of 10 mL/min; a subject's last observed creatinine value from month 3 on was used for the remainder of subjects with missing creatinine at month 12 (n = 11, 12, 15, and 19 for Groups A, B, C, and D, respectively). Weight was also imputed in the calculation of estimated GFR, if missing.

† Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

Table: Incidence of BPAR, Graft loss, Death or Loss to Follow-up at 12 months (Study 1)

	Group A N=390	**Group B N=399**	**Group C N=401**	**Group D N=399**
Overall failure	141 (36.2%)	126 (31.6%)	82 (20.4%)	185 (46.4%)
Components of efficacy failure				
BPAR	113 (29.0%)	106 (26.6%)	60 (15.0%)	152 (38.1%)
Graft loss excluding death	28 (7.2%)	20 (5.0%)	12 (3.0%)	30 (7.5%)
Mortality	13 (3.3%)	7 (1.8%)	11 (2.7%)	12 (3.0%)
Lost to follow-up	5 (1.3%)	7 (1.8%)	5 (1.3%)	6 (1.5%)
Treatment Difference of efficacy failure compared to Group C (99.2% CI*)	15.8% (7.1%, 24.3%)	11.2% (2.7%, 19.5%)	-	26.0% (17.2%, 34.7%)

Key: Group A = CsA/MMF/CS, B = CsA/MMF/CS/Daclizumab, C = Tac/MMF/CS/Daclizumab, and D = Siro/MMF/CS/Daclizumab

*Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

The protocol-specified target tacrolimus trough concentrations ($C_{trough,Tac}$) were 3-7 ng/mL; however, the observed median $C_{troughs,Tac}$ approximated 7 ng/mL throughout the 12-month trial.

Approximately 80% of patients maintained tacrolimus whole blood concentrations between 411 ng/mL through 1-year post-transplant.

Table: Tacrolimus Whole Blood Trough Concentration Range (Study 1)

Time	Median (P10-P90*) tacrolimus whole blood trough concentration range (ng/mL)
Day 30 (N = 366)	6.9 (4.4 – 11.3)
Day 90 (N = 351)	6.8 (4.1 – 10.7)
Day 180 (N = 355)	6.5 (4.0 – 9.6)
Day 365 (N = 346)	6.5 (3.8 – 10.0)

*10 to 90th Percentile: range of $C_{trough,Tac}$ that excludes lowest 10% and highest 10% of $C_{trough,Tac}$

The protocol-specified target cyclosporine trough concentrations ($C_{trough,CsA}$) for Group B were 50-100 ng/mL; however, the observed median $C_{troughs,CsA}$ approximated 100 ng/mL throughout the 12-month trial. The protocol-specified target $C_{troughs,CsA}$ for Group A were 150-300 ng/mL for the first 3 months and 100-200 ng/mL from month 4 to month 12; the observed median $C_{troughs,CsA}$ approximated 225 ng/mL for the first 3 months and 140 ng/mL from month 4 to month 12. While patients in all groups started MMF at 1 gram twice daily, the MMF dose was reduced to less than 2 g per day in 63% of patients in the tacrolimus treatment arm by month 12; approximately 50% of these MMF dose reductions were due to adverse reactions. By comparison, the MMF dose was reduced to less than 2 g per day in 49% and 45% of patients in the two cyclosporine arms (Group A and Group B, respectively), by month 12 and approximately 40% of MMF dose reductions were due to adverse reactions.

Table: MMF Dose Over Time in tacrolimus/MMF (Group C) (Study 1)

Time period (Days)	Time-averaged MMF dose (grams per day)*		
	Less than 2.0	2.0	Greater than 2.0

0-30 (N = 364)	37%	60%	2%
0-90 (N = 373)	47%	51%	2%
0-180 (N = 377)	56%	42%	2%
0-365 (N = 380)	63%	36%	1%
Key: Time-averaged MMF dose = (total MMF dose)/(duration of treatment)			

* Percentage of patients for each time-averaged MMF dose range during various treatment periods. Administration of 2 g per day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

In a second randomized, open-label, multicenter trial (Study 2), 424 kidney transplant patients received tacrolimus (N = 212) or cyclosporine (N = 212) in combination with MMF 1 gram twice daily, basiliximab induction, and corticosteroids. In this trial, the rate for the combined endpoint of BPAR, graft failure, death, and/or lost to follow-up at 12 months in the tacrolimus/MMF group was similar to the rate in the cyclosporine/MMF group. There was, however, an imbalance in mortality at 12 months in those patients receiving tacrolimus/MMF (4%) compared to those receiving cyclosporine/MMF (2%), including cases attributed to over-immunosuppression.

Table: Incidence of BPAR, Graft Loss, Death, or Loss to Follow-up at 12 Months (Study 2)

	Tacrolimus/MMF (N=212)	Cyclosporine/MMF (N=212)
Overall failure	32 (15.1%)	36 (17.0%)
Components of efficacy failure		

BPAR	16 (7.5%)	29 (13.7%)
Graft loss excluding death	6 (2.8%)	4 (1.9%)
Mortality	9 (4.2%)	5 (2.4%)
Lost to follow-up	4 (1.9%)	1 (0.5%)
Treatment Difference of efficacy failure compared to tacrolimus/MMF group (95% CI*)		1.9% (-5.2%, 9.0%)

* 95% confidence interval calculated using Fisher's Exact Test.

The protocol-specified target tacrolimus whole blood trough concentrations ($C_{trough,Tac}$) in Study
2 were 7-16 ng/mL for the first three months and 5-15 ng/mL thereafter. The observed median $C_{troughs,Tac}$ approximated 10 ng/mL during the first three months and 8 ng/mL from month 4 to month 12. Approximately 80% of patients maintained tacrolimus whole blood trough concentrations between 6 to 16 ng/mL during months 1 through 3 and, then, between 5 to 12 ng/mL from month 4 through 1 year.

Table: Tacrolimus Whole Blood Trough Concentration Range (Study 2)

Time	Median (P10-P90*) tacrolimus whole blood trough concentration range (ng/mL)
Day 30 (N = 174)	10.5 (6.3 – 16.8)
Day 60 (N = 179)	9.2 (5.9 – 15.3)
Day 120 (N = 176)	8.3 (4.6 – 13.3)
Day 180 (N = 171)	7.8 (5.5 – 13.2)
Day 365 (N = 178)	7.1 (4.2 – 12.4)

*10 to 90th Percentile: range of $C_{trough,Tac}$ that excludes lowest 10% and highest 10% of $C_{trough,Tac}$.

The protocol-specified target cyclosporine whole blood concentrations ($C_{trough,CsA}$) were 125 to 400 ng/mL for the first three months, and 100 to 300 ng/mL thereafter. The observed median $C_{troughs,CsA}$ approximated 280 ng/mL during the first three months and 190 ng/mL from month 4 to month 12. Patients in both groups started MMF at 1 gram twice daily. The MMF dose was reduced to less than 2 grams per day by month 12 in 62% of patients in the tacrolimus/MMF group and in 47% of patients in the cyclosporine/MMF group. Approximately 63% and 55% of these MMF dose reductions were because of adverse reactions in the tacrolimus/MMF group and the cyclosporine/MMF group, respectively.

Table: MMF Dose Over Time in the tacrolimus/MMF Group (Study 2)

Time period (Days)	Time-averaged MMF dose (grams per day)*		
	Less than 2.0	2.0	Greater than 2.0
0-30 (N = 212)	25%	69%	6%
0-90 (N = 212)	41%	53%	6%
0-180 (N = 212)	52%	41%	7%
0-365 (N = 212)	62%	34%	4%
Key: Time-averaged MMF dose = (total MMF dose)/(duration of treatment)			

* Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two grams per day of time averaged MMF dose means that the MMF dose was not reduced in those patients during the treatment periods.

Liver transplantation

The safety and efficacy of tacrolimus-based immunosuppression following orthotopic liver transplantation were assessed in two prospective, randomized, non-blinded multicenter trials. The active control groups were treated with a cyclosporine-based immunosuppressive regimen

(CsA/AZA). Both trials used concomitant adrenal corticosteroids as part of the immunosuppressive regimens. These trials compared patient and graft survival rates at 12 months following transplantation.

In one trial, 529 patients were enrolled at 12 clinical sites in the United States; prior to surgery, 263 were randomized to the tacrolimus-based immunosuppressive regimen and 266 to the CsA/AZA. In 10 of the 12 sites, the same CsA/AZA protocol was used, while 2 sites used different control protocols. This trial excluded patients with renal dysfunction, fulminant hepatic failure with Stage IV encephalopathy, and cancers; pediatric patients (≤ 12 years old) were allowed. In the second trial, 545 patients were enrolled at 8 clinical sites in Europe; prior to surgery, 270 were randomized to the tacrolimus-based immunosuppressive regimen and 275 to CsA/AZA. In this trial, each center used its local standard CsA/AZA protocol in the active-control arm. This trial excluded pediatric patients, but did allow enrollment of subjects with renal dysfunction, fulminant hepatic failure in Stage IV encephalopathy, and cancers other than primary hepatic with metastases.

One-year patient survival and graft survival in the tacrolimus-based treatment groups were similar to those in the CsA/AZA treatment groups in both trials. The overall 1-year patient survival (CsA/AZA and tacrolimus-based treatment groups combined) was 88% in the U.S. trial and 78% in the European trial. The overall 1-year graft survival (CsA/AZA and tacrolimus-based treatment groups combined) was 81% in the U.S. trial and 73% in the European trial. In both trials, the median time to convert from IV to oral tacrolimus dosing was 2 days.

Although there is a lack of direct correlation between tacrolimus concentrations and drug efficacy, data from clinical trials of liver transplant patients have shown an increasing incidence of adverse reactions with increasing trough blood concentrations. Most patients are stable when trough whole blood concentrations are maintained between 5 to 20 ng/mL. Long-term post-transplant patients are often maintained at the low end of this target

range. Data from the U.S. clinical trial show that the median trough blood concentrations, measured at intervals from the second week to one year posttransplantation, ranged from 9.8 ng/mL to 19.4 ng/mL.

Heart transplantation

Two open-label, randomized, comparative trials evaluated the safety and efficacy of tacrolimus-based and cyclosporine based immunosuppression in primary orthotopic heart transplantation. In a trial conducted in Europe, 314 patients received a regimen of antibody induction, corticosteroids, and azathioprine in combination with tacrolimus or cyclosporine modified for 18 months. In a 3-arm trial conducted in the U.S., 331 patients received corticosteroids and tacrolimus plus sirolimus, tacrolimus plus mycophenolate mofetil (MMF) or cyclosporine modified plus MMF for 1 year.

In the European trial, patient/graft survival at 18 months post-transplant was similar between treatment arms, 92% in the tacrolimus group and 90% in the cyclosporine group. In the U.S. trial, patient and graft survival at 12 months was similar with 93% survival in the tacrolimus plus MMF group and 86% survival in the cyclosporine modified plus MMF group. In the European trial, the cyclosporine trough concentrations were above the pre-defined target range (i.e., 100 to 200 ng/mL) at Day 122 and beyond in 32% to 68% of the patients in the cyclosporine treatment arm, whereas the tacrolimus trough concentrations were within the pre-defined target range (i.e., 5 to 15 ng/mL) in 74% to 86% of the patients in the tacrolimus treatment arm. Data from this European trial indicate that from 1 week to 3 months posttransplant, approximately 80% of patients maintained trough concentrations between 8 to 20 ng/mL and, from 3 months through 18 months post-transplant, approximately 80% of patients maintained trough concentrations between 6 to 18 ng/mL.

The U.S. trial contained a third arm of a combination regimen of sirolimus, 2 mg per day, and full-dose tacrolimus; however, this regimen was associated with increased risk of wound-healing complications, renal function

impairment, and insulin-dependent post-transplant diabetes mellitus, and is not recommended.

5.2 Pharmacokinetic properties:

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. *Food effects*

The rate and extent of tacrolimus absorption were greatest under fasted conditions. The presence and composition of food decreased both the rate and extent of tacrolimus absorption. When given immediately following the meal, mean C_{max} was reduced 71%, and mean AUC was reduced 39%, relative to the fasted condition. When administered 1.5 hours following the meal, mean C_{max} was reduced 63%, and mean AUC was reduced 39%, relative to the fasted condition.

Distribution

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration.

Elimination

Metabolism

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P450 system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation *in vitro*. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In *in vitro* studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

Excretion

In man, less than 1% of the dose administered is excreted unchanged in urine.

Specific population

Pediatric Patients

Tacrolimus capsules Pharmacokinetics in Pediatric Patients

Pharmacokinetics of tacrolimus have been studied in liver transplantation patients, 0.7 to 13.2 years of age. Following IV administration of a 0.037 mg/kg/day dose to 12 pediatric patients, mean terminal half-life, volume of distribution and clearance were 11.5 ± 3.8 hours, 2.6 ± 2.1 L/kg and 0.138 ± 0.071 L/hr/kg, respectively. Following oral administration to 9 patients, mean AUC and C_{max} were 337 ± 167 ng·hr/mL and 48.4 ± 27.9 ng/mL, respectively. The absolute bioavailability was 31 ± 24%.

Pharmacokinetics of tacrolimus have also been studied in kidney transplantation patients, 8.2 ± 2.4 years of age. Following IV infusion of a 0.06 mg/kg/day to 12 pediatric patients (8 male and 4 female), mean terminal half-life and clearance were 10.2 ± 5.0 hours and 0.12 ± 0.04 L/hr/kg, respectively. Following oral administration to the same patients, mean AUC and Cmax were 181 ± 65 ng·hr/mL and 30 ± 11 ng/mL, respectively. The absolute bioavailability was 19 ± 14%.

Whole blood trough concentrations from 31 patients less than 12 years old showed that pediatric patients needed higher doses than adults to achieve similar tacrolimus trough concentrations.

Patients with Renal Impairment

Tacrolimus pharmacokinetics, following a single IV administration, were determined in 12 patients (7 not on dialysis and 5 on dialysis, serum creatinine of 3.9 ± 1.6 and 12.0 ± 2.4 mg/dL, respectively) prior to their kidney transplant. The pharmacokinetic parameters obtained were similar for both groups. The mean clearance of tacrolimus in patients with renal dysfunction was similar to that in normal volunteers.

Patients with Hepatic Impairment

Tacrolimus pharmacokinetics have been determined in six patients with mild hepatic dysfunction (mean Pugh score: 6.2) following single IV and oral administrations. The mean clearance of tacrolimus in patients with mild hepatic dysfunction was not substantially different from that in normal volunteers. Tacrolimus pharmacokinetics were studied in 6 patients with severe hepatic dysfunction (mean Pugh score: > 10). The mean clearance was substantially lower in patients with severe hepatic dysfunction, irrespective of the route of administration.

Male and Female Patients

A formal trial to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted, however, there was no difference in dosing by gender in the kidney transplant trial. A retrospective comparison of pharmacokinetics in healthy volunteers, and in kidney, liver, and heart transplant patients indicated no gender-based differences.

Racial or Ethnic Groups

The pharmacokinetics of tacrolimus have been studied following single IV and oral administration of tacrolimus to 10 African-American, 12 Latino-American, and 12 Caucasian healthy volunteers. There were no significant pharmacokinetic differences among the three ethnic groups following a 4-hour IV infusion of 0.015 mg/kg. There was no significant difference in mean terminal $t_{1/2}$ among the three ethnic groups (range from approximately 25 to 30 hours). A retrospective comparison of African-American and Caucasian kidney transplant patients indicated that African-American patients required higher tacrolimus doses to attain similar trough concentrations.

5.3 Preclinical safety data

Carcinogenesis

Carcinogenicity studies were conducted in male and female rats and mice. In the 80-week mouse oral study and in the 104-week rat oral study, no relationship of tumor incidence to tacrolimus dosage was found. The highest

dose used in the mouse was 3.0 mg/kg/day (0.9 to 2.2 times the AUC at clinical doses of 0.075 to
0.2 mg/kg/day) and in the rat was 5.0 mg/kg/day (0.265 to 0.65 times the AUC at clinical doses of 0.075 to
0.2 mg/kg/day).

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03% - 3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m2 /day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high-dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high-dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment). The relevance of topical administration of tacrolimus in the setting of systemic tacrolimus use is unknown.

The implications of these carcinogenicity studies to the human condition are limited; doses of tacrolimus were administered that likely induced immunosuppression in these animals, impairing their immune system's ability to inhibit unrelated carcinogenesis.

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, subcutaneously administered to male rats at paternally toxic doses of 2 mg/kg/day (1.6 to 4.3 times the recommended clinical dose range

[0.2 to 0.075 mg/kg/day] on a mg/m2 basis) or 3 mg/kg/day (2.4 to 6.4 times the recommended clinical dose range), resulted in a dose-related decrease in sperm count. Tacrolimus, administered orally at 1.0 mg/kg (0.8 to 2.2 times the clinical dose range) 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. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre- and postimplantation loss and increased numbers of undelivered and nonviable pups. When administered 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.

In acute oral and IV toxicity studies, mortalities were seen at or above the following doses: in adult rats, 52 times the recommended human oral dose; in immature rats, 16 times the recommended oral dose; and in adult rats, 16 times the recommended human IV dose (all based on body surface area corrections).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

- Hypromellose
- Croscarmellose Sodium
- Ethanol
- Lactose Monohydrate
- Croscarmellose Sodium
- Croscarmellose Sodium
- Magnesium Stearate (Veg # 2257)
- EHG Capsule “4” White

6.2 Incompatibilities

None of the In-active ingredients of the formulation have been known to exhibit incompatibility with the Active ingredient.

6.3 Shelf-life

24 Months

6.4 Special precautions for storage

Store in a dry place, below 25°C. Protect from light.

6.5 Nature and contents of container

10 capsules are packed in Alu-Alu blister pack. 1 such blister is packed in a carton along with a package insert.

6.6 Instructions for use and handling

Keep away from the reach of children

7 MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Ltd.
Lane No.3, Phase –II, SIDCO Industrial Complex,
Bari-Brahmana, Jammu (J&K) -181133

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