Panacea Biotec
Innovation in support of life

For the use of a Nephrologist/Transplant Surgeon or a Hospital or a Laboratory only

Tacrolimus Capsules IP

PanGraf® 0.25 / 0.5 / 1.0 / 2.0 / 5.0

BOX WARNING MALIGNANCIES AND SERIOUS INFECTIONS

- **Increased risk of development of lymphoma and other malignancies, particularly of the skin, due to immunosuppression**
- **Increased susceptibility to bacterial, viral, fungal, and protozoal infections, including opportunistic infections**
- **Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Pangraf. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient**

DESCRIPTION

Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis.* Chemically, tacrolimus is [3S[3R*[E(1S*,3S*,4S*)], 4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*, 18S*, 19S*,26aR*]] 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18 -tetramethyl-8-(2-propenyl)-15,19epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclotricosine-1,7,20,21 (4H,23H)-tetrone, monohydrate. Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}.H_2O$ and a formula weight of 822.03.

PanGraf 0.25

Orange/Orange size “5” hard gelatin capsules printed with “PBT” and “0.25” as per approved text and design in red ink on cap and body, respectively, containing white to off-white granular powder.

PanGraf 0.5

Light yellow/Light yellow size “5” hard gelatin capsules printed with “PBT” and “0.5” as per approved text and design in red ink on cap and body, respectively, containing white to off-white granular powder.

PanGraf 1.0

White/White size “5” hard gelatin capsules printed with “PBT” and ”1.0” as per approved text and design in red ink on cap and body, respectively, containing white to off-white granular powder.

PanGraf 2.0

Grey/Grey size “5” hard gelatin capsules printed with “PBT” and ”2.0” as per approved text and design in red ink on cap and body, respectively, containing white to off-white granular powder.

PanGraf 5.0

Pink/Pink size “4” hard gelatin capsules printed with “PBT” and “5.0” as per approved text and design in red ink on cap and body, respectively, containing white to off-white granular powder.

COMPOSITION

Tacrolimus Capsules IP 0.25 mg
PanGraf 0.25
Each hard gelatin capsule contains:
Tacrolimus IP 0.25 mg
Approved colours used in capsule shells

Tacrolimus Capsules IP 0.5 mg
PanGraf 0.5
Each hard gelatin capsule contains:
Tacrolimus IP 0.5 mg
Approved colours used in capsule shells

Tacrolimus Capsules IP 1.0 mg
PanGraf 1.0
Each hard gelatin capsule contains:
Tacrolimus IP 1.0 mg
Approved colours used in capsule shells

Tacrolimus Capsules IP 2.0 mg
PanGraf 2.0
Each hard gelatin capsule contains:
Tacrolimus IP 2.0 mg
Approved colours used in capsule shells

Tacrolimus Capsules IP 5.0 mg
PanGraf 5.0
Each hard gelatin capsule contains:
Tacrolimus IP 5.0 mg
Approved colours used in capsule shells

DOSAGE FORM

Hard gelatin capsule

INDICATIONS

Tacrolimus is indicated for prophylaxis of organ rejection in patient receiving allogenic kidney transplant.

DOSE AND METHOD OF ADMINISTRATION

PanGraf dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring. If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered. It is recommended that the oral daily dose be administered in two divided doses (e.g. morning and evening). Capsules should be taken immediately following removal from the blister. Patients should be advised not to swallow the desiccant. The capsules should be swallowed with fluid (preferably water). 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.

Dosage recommendations - Kidney transplantation

Prophylaxis of transplant rejection adults

Oral tacrolimus therapy should commence at 0.20 - 0.30 mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence within 24 hours after the completion of surgery. If the clinical condition of the patient allows oral dosing.

Prophylaxis of transplant rejection children

An initial oral dose of 0.30mg/kg/day should be administered in two divided doses (e.g. morning and evening). If the clinical condition of the patient allows oral dosing.

Dose adjustment during post-transplant period in adults and children

Tacrolimus doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus-based dual-therapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy adults and children

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

For conversion to tacrolimus, treatment should begin with the initial oral dose recommended for primary immunosuppression.

Dosage adjustments in specific patient populations

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

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

Paediatric patients: In general, paediatric patients require doses 1½ - 2 times higher than the adult doses to achieve similar blood levels.

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

Conversion from One Immunosuppressive Regimen to Another

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.

Blood Concentration 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. 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.

Whole blood is the matrix of choice and specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-coagulant. Heparin anti-coagulation is not recommended because of the tendency to form clots on storage.

USE IN SPECIAL POPULATIONS

Pregnancy *(Category C)*

There are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta. The use of tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. Tacrolimus should be used during pregnancy only if the potential benefit to the mother justifies potential risk to the fetus.

Lactation

Since tacrolimus is excreted in human milk, nursing should be avoided.

Pediatric Patients

Experience with tacrolimus in pediatric kidney transplant patients is limited. Pediatric patients generally required higher doses of tacrolimus to maintain blood trough concentrations of tacrolimus similar to adult patients.

CONTRA-INDICATIONS

Hypersensitivity to tacrolimus or other macrolides. Hypersensitivity to any of the excipients. Hypersensitivity symptoms reported include dyspnea, rash, pruritus, and acute respiratory distress syndrome.

WARNINGS

Management of Immunosuppression

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

Malignancy and Lymphoproliferative Disorders

As in patients receiving other immunosuppressants, patients receiving 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. A lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. The risk of LPD appears greatest in young children who are at risk for primary EBV infection while immunosuppressed or who are switched to tacrolimus following long-term immunosuppression therapy. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Latent Viral Infections: Patients treated with immunosuppressants, including tacrolimus are at increased risk of 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 renal function or neurological symptoms.

Cytomegalovirus (CMV) Infections

Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing CMV viremia and CMV disease. The risk of CMV disease is highest among transplant recipients seronegative for CMV at time of transplant who receive a graft from a CMV seropositive donor. Therapeutic approaches to limiting CMV disease exist and should be routinely provided. Patient monitoring may help detect patients at risk for CMV disease. Consideration should be given to reducing the amount of immunosuppression in patients who develop CMV viremia and/or CMV disease.

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. Blood glucose concentrations should be monitored closely in patients using 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. If PRCA is diagnosed, discontinuation of tacrolimus should be considered.

Nephrotoxicity

Tacrolimus can cause nephrotoxicity, particularly when used in high doses. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Care should be taken in using tacrolimus with other nephrotoxic drugs. In particular, to avoid excess nephrotoxicity, tacrolimus should not be used simultaneously with cyclosporine. Tacrolimus or cyclosporine should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated tacrolimus or cyclosporine concentrations, dosing with the other drug usually should be further delayed.

Hyperkalemia

Mild to severe hyperkalemia was reported with the use of tacrolimus. Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during tacrolimus therapy.

Neurotoxicity

Tacrolimus can cause neurotoxicity, particularly when used in high doses. 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.

Tacrolimus in Combination with Sirolimus

The use of full-dose tacrolimus with sirolimus (2 mg per day) in heart transplant recipients was associated with increased risk of wound healing complications, renal function impairment, and insulin-dependent post-transplant diabetes mellitus, and is not recommended.

Anaphylactic Reactions: A few patients receiving tacrolimus injection have experienced anaphylactic reactions. Although the exact cause of these reactions is not known, other drugs with castor oil derivatives in the formulation have been associated with anaphylaxis in a small percentage of patients. Because of this potential risk of anaphylaxis, tacrolimus injection should be reserved for patients who are unable to take tacrolimus capsules.

PRECAUTION

Hypertension

Hypertension is a common adverse effect of tacrolimus therapy. Mild or moderate hypertension is more frequently reported than severe hypertension. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating tacrolimus associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction.

Renally and Hepatically Impaired Patients

For patients with renal insufficiency some evidence suggests that lower doses should be used.

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 levels 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.

Myocardial Hypertrophy

Myocardial hypertrophy has been reported in association with the administration of tacrolimus, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. Hypertrophy has been observed in infants, children and adults. 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.

Laboratory Tests

Serum creatinine, potassium, and fasting glucose should be assessed regularly. Routine monitoring of metabolic and hematologic systems should be performed as clinically warranted.

DRUG INTERACTION

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering tacrolimus with drugs that may be associated with

Product Name	Pangraf	**Change Control No.: BCC323/16**	
Item Code	PPIP022E	Colours	■ Black
Size	300 x 220 mm	Revision No.:	
Market	Domestic		

renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, and cisplatin. Initial clinical experience with the co-administration of tacrolimus and cyclosporine resulted in additive/synergistic nephrotoxicity. Patients switched from cyclosporine to tacrolimus should receive the first tacrolimus dose no sooner than 24 hours after the last cyclosporine dose. Dosing may be further delayed in the presence of elevated cyclosporine levels.

Drugs that May Alter Tacrolimus Concentrations

Calcium Channel Blockers: diltiazem, nicardipine, nifedipine, verapamil
Antifungal Agents: clotrimazole, fluconazole, itraconazole, ketoconazole, voriconazole
Macrolide Antibiotics: clarithromycin, erythromycin, troleandomycin
Gastrointestinal Prokinetic Agents: cisapride, metcolopramide
Other Drugs: bromocriptine, chloramphenicol, cimetidine, cyclosporine, danazol, ethinyl estradiol, methylprednisolone, lansoprazolec, omeprazole, protease inhibitors, nefazodone, magnesium-aluminum hydroxide

Drugs That May Decrease Tacrolimus Blood Concentrations

Anticonvulsants: carbamazepine, phenobarbital, phenytoin
Antimicrobials: rifabutin, caspofungin, rifampin
Herbal Preparations: St. John's Wort
Other Drugs: sirolimus, magnesium-aluminum-hydroxide

Interaction studies with drugs used in HIV therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir) or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are administered concomitantly with tacrolimus.
Tacrolimus may affect the pharmacokinetics of other drugs (e.g., phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided.

Other Drug Interactions

Immunosuppressants may affect vaccination. Therefore, during treatment with tacrolimus, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and TY 21a typhoid.
At a given MMF dose, mycophenolic acid (MPA) exposure is higher with tacrolimus co-administration than with cyclosporine co-administration due to the differences in the interruption of the enterohepatic recirculation of MPA. Clinicians should be aware that there is also a potential for increased MPA exposure after crossover from cyclosporine to tacrolimus in patients concomitantly receiving MMF or MPA.

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).

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

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

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

Ear and labyrinth disorders

Common: tinnitus
Uncommon: hypoacusis
Rare: deafness neurosensory
Very rare: hearing impaired

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, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastrooesophageal reflux disease, impaired gastric emptying
Rare: subileus, pancreatic pseudocyst

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

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 cramps, pain in limb, back pain
Uncommon: joint disorders

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, anorexia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities
Uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

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.

Injury, poisoning and procedural complications

Common: primary graft dysfunction
Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. A number of associated cases of transplant rejection have been reported (frequency cannot be estimated from available data).
Neoplasms benign, malignant and unspecified (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.

Vascular disorders

Very common: hypertension
Common: haemorrhage, thrombembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
Uncommon: infarction, venous thrombosis deep limb, shock

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, mobility decreased, ulcer
Very rare: fat tissue increased

Immune system disorders

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus.

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

Reproductive system and breast disorders

Uncommon: dysmenorrhoea and uterine bleeding

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

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 or -diafiltration have been effective in reducing toxic concentrations. In cases of oral intoxication, gastric lavage and/or the use of adsorbents (such as activated charcoal) may be helpful, if used shortly after intake.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Mechanism of action

At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of lymphokine genes.
Tacrolimus is a highly potent immunosuppressive agent and has proven activity in both in vitro and in vivo experiments.
In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines (such as interleukins-2, -3, and γ-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 tacrolimus in blood are achieved in approximately 1 - 3 hours. In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively 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 the majority of patients.
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.

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.

Metabolism

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 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

Following intravenous and oral administration of ^{14}C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2% of the radioactivity was eliminated in the urine. Less than 1% of unchanged tacrolimus was detected in the urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

Special Populations

Pediatric: Children require higher mg/kg doses than adults because of higher clearance than adults.
Hepatic Impairment: The mean clearance of tacrolimus in patients with mild hepatic dysfunction was not substantially different from that in normal volunteers. The mean clearance was substantially lower in patients with severe hepatic dysfunction, irrespective of the route of administration.
Renal Insufficiency

The mean clearance of tacrolimus in patients with renal dysfunction was similar to that in normal volunteers.

Race

A formal study to evaluate the pharmacokinetic disposition of tacrolimus in black transplant patients has not been conducted. However, a retrospective comparison of black and Caucasian kidney transplant patients indicated that black patients required higher tacrolimus doses to attain similar trough concentrations.

Gender

A formal study 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.

SHELF-LIFE

24 months from the date of manufacturing.

PACKAGING INFORMATION

PanGraf 0.25 : 10 Capsules in a Alu/Alu blister strip.
PanGraf 0.5 : 10 Capsules in a Alu/Alu blister strip.
PanGraf 1.0 : 10 Capsules in a Alu/Alu blister strip.
PanGraf 2.0 : 10 Capsules in a Alu/Alu blister strip.
PanGraf 5.0 : 10 Capsules in a Alu/Alu blister strip.

STORAGE INSTRUCTIONS

Store at a temperature not more than 25°C, protect from light and moisture.
KEEP THE MEDICINE OUT OF REACH OF CHILDREN.

For more information and details contact:
Panacea Biotec Ltd.
B-1Ext./A-27, Mohan Co-op. Indl. Estate,
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PPIP022E

Product Name	Pangraf	**Change Control No.: BCC323/16**
Item Code	PPIP022E	Colours ■ Black
Size	300 x 220 mm	Revision No.:
Market	Domestic	