For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Tacrolimus Capsule IP 0.5 mg, 1 mg, 5 mg

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 tacrolimus. 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.**

COMPOSITION

Each hard gelatin capsule contains:
Tacrolimus IP…….0.5 mg/ 1 mg/ 5 mg
Excipients……. q.s.
Approved colours used in the capsule shell.

DESCRIPTION

Tacrolimus is available for oral administration as capsules (tacrolimus capsules USP) containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus USP.
Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [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-3-methoxycyclohexyl)-1methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-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. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

CLINICAL PHARMACOLOGY

Mechanism of Action

Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear

component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

Pharmacokinetics

Absorption

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. Bile flow does not influence the absorption of tacrolimus

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 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 faeces, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

INDICATION

For the prophylaxis of organ rejection in patients receiving allogenic liver, kidney or heart transplants.

It is recommended that tacrolimus be used concomitantly with azathioprine or mycophenolate mofetil (MMF) and adrenal corticosteroids.

DOSAGE AND ADMINISTRATION

Dosage in Adult Kidney, Liver or Heart Transplant Patients

The initial oral dosage recommendations for adult patients with kidney, liver, or heart transplants along with recommendations for whole blood trough concentrations are shown in table below.

Patient population	**Recommended tacrolimus Initial Oral Dosage** Note: daily doses should be administered as two divided doses, every 12 hours	**Observed Tacrolimus Whole Blood Trough Concentrations**

Adult kidney transplant patients In combination with azathioprine In combination with MMF/IL-2 receptor antagonist[a]	 0.2 mg/kg/day 0.1 mg/kg/day	 month 1-3: 7-20 ng/mL month 4-12: 5-15 ng/mL month 1-12: 4-11 ng/ml
Adult liver transplant patients	0.10-0.15 mg/kg/day	month 1-12: 5-20 ng/mL
Adult heart transplant patients	0.075 mg/kg/day	month 1-3: 10-20 ng/mL month ≥4: 5-15 ng/mL

The initial dose of tacrolimus 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 tacrolimus may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered.
Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower tacrolimus dosages than the recommended initial dosage may be sufficient as maintenance therapy. Adjunct therapy with adrenal corticosteroids is recommended early post-transplant.

Initial Dose – Injection

In a patient receiving an IV infusion, the first dose of oral therapy should be given 8-12 hours after discontinuing the IV infusion.
The recommended starting dose of tacrolimus injection is 0.03-0.05 mg/kg/day in kidney and liver transplant and 0.01 mg/kg/day in heart transplant given as a continuous IV infusion. Adult patients should receive doses at the lower end of the dosing range. Concomitant adrenal corticosteroid therapy is recommended early post-transplantation.

Paediatric population

The initial oral dosage recommendations for pediatric patients with liver transplants along with recommendations for whole blood trough concentrations are shown below.

Patient population	**Recommended tacrolimus initial oral dosage** Note: daily doses should be administered as two divided doses, every 12 hours.	**Observed tacrolimus whole blood trough concentrations**
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	Month 1-12: 5-20 ng/mL

Pediatric liver transplantation patients without pre-existing renal or hepatic dysfunction have required and tolerated higher doses than adults to achieve similar blood concentrations.

Experience in pediatric kidney and heart transplantation patients is limited.

CONTRAINDICATIONS

Tacrolimus is contraindicated in patients with a hypersensitivity to tacrolimus. Hypersensitivity symptoms reported include dyspnea, rash, pruritus, and acute respiratory distress syndrome.

WARNINGS AND PRECAUTIONS

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.

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, exposure to sunlight and UV light should be limited by wearing protective clothing and using a 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.

Serious Infections

Patients receiving immunosuppressants, including vingraf, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

Polyoma Virus Infections

Patients receiving immunosuppressants, including tacrolimus, are at increased risk for opportunistic infections, including polyoma virus infections. Polyoma virus infections in transplant patients may have serious, and sometimes fatal, outcomes. These include polyoma virus-associated nephropathy (PVAN), mostly due to BK virus infection, and JC virus-associated progressive multifocal leukoencephalopathy (PML) which have been observed in patients receiving tacrolimus. PVAN is associated with serious outcomes, including deteriorating renal function and kidney graft loss. Patient monitoring may help detect patients at risk for PVAN. Cases of PML have been reported in patients treated with tacrolimus. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Reductions in immunosuppression should be considered for patients who develop evidence of PVAN or PML. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft.

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.

Nephrotoxicity

Tacrolimus, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity, particularly when used in high doses. Acute nephrotoxicity is most often related to vasoconstriction of the afferent renal arteriole, is characterized by increasing serum creatinine, hyperkalemia, and/or a decrease in urine output, and is typically reversible. Chronic calcineurin inhibitor nephrotoxicity is associated with increased serum creatinine, decreased kidney graft life, and characteristic histologic changes observed on renal biopsy; the changes associated with chronic calcineurin-inhibitor nephrotoxicity are typically progressive. 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.

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 renal dysfunction. These include, but are not limited to, aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors (e.g., tenofovir) and protease inhibitors (e.g., ritonavir, indinavir). Similarly, care should be exercised when administering with CYP3A4 inhibitors such as antifungal drugs (e.g., ketoconazole), calcium channel blockers (e.g., diltiazem, verapamil), and macrolide antibiotics (e.g., clarithromycin, erythromycin, troleandomycin) which will result in increased tacrolimus whole blood concentrations due to inhibition of tacrolimus metabolism.

Neurotoxicity

Tacrolimus may cause a spectrum of neurotoxicities, particularly when used in high doses. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, and coma. Patients treated with tacrolimus have been reported to develop PRES. Symptoms indicating PRES include headache, altered mental status, seizures, visual disturbances and hypertension. Diagnosis may be confirmed by radiological procedure. If PRES is suspected or diagnosed, blood pressure control should be maintained and immediate reduction of immunosuppression is advised. This syndrome is characterized by reversal of symptoms upon reduction or discontinuation of immunosuppression. Coma and delirium, in the absence of PRES, have also been associated with high plasma concentrations of tacrolimus. Seizures have occurred in adult and pediatric patients receiving tacrolimus. Less severe neurotoxicities, include tremors, parathesias, headache, and other changes in motor function, mental status, and sensory function. Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment.

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.

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.

Use with Sirolimus

The safety and efficacy of tacrolimus with sirolimus has not been established in kidney transplant patients.

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

Use with Strong Inhibitors and Inducers of CYP3A

Co-administration with strong CYP3A4-inhibitors (e.g., ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong inducers (e.g., rifampin, rifabutin) is not recommended without close monitoring of tacrolimus whole blood trough concentrations.

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

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.

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.

ADVERSE REACTIONS

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).

Very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, insomnia, tremor, headache, hypertension, diarrhoea, nausea, renal impairment
Common: anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal, hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities, anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders, seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders, vision blurred, photophobia, eye disorders, tinnitus, ischaemic coronary artery disorders, tachycardia, haemorrhage, thrombembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders, dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations, 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, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis, pruritus, rash, alopecias, acne, sweating increased, arthralgia, muscle spasms, pain in limb, back pain, renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy, toxic, urinary abnormalities, bladder and urethral symptoms, asthenic conditions, febrile disorders, oedema, pain and discomfort, body temperature perception disturbed, hepatic enzymes and function abnormalities, blood alkaline phosphatase, increased, weight increased, primary graft dysfunction
Uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia, dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia, psychotic disorder, coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia, cataract, hypoacusis, ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, infarction, venous thrombosis deep limb, shock Respiratory, thoracic and mediastinal disorders, ileus paralytic, acute and chronic pancreatitis, gastrooesophageal reflux disease, impaired gastric emptying, dermatitis, photosensitivity, joint disorders, anuria, haemolytic uraemic syndrome, dysmenorrhoea and uterine bleeding, multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, amylase increased, ECG investigations abnormal, heart rate and pulse investigations abnormal, weight decreased, blood lactate dehydrogenase increased

DRUG INTERACTIONS

Since tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations.

Mycophenolic Acid Products

With a given dose of mycophenolic acid (MPA) products, exposure to MPA is higher with tacrolimus co-administration than with cyclosporine co-administration because cyclosporine

interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Clinicians should be aware that there is also a potential for increased MPA exposure after crossover from cyclosporine to tacrolimus in patients concomitantly receiving MPA-containing products.

Grapefruit Juice

Grapefruit juice inhibits CYP3A-enzymes resulting in increased tacrolimus whole blood trough concentrations, and patients should avoid eating grapefruit or drinking grapefruit juice with tacrolimus.

Protease Inhibitors

Most protease inhibitors inhibit CYP3A enzymes and may increase tacrolimus whole blood concentrations. It is recommended to avoid concomitant use of tacrolimus with nelfinavir unless the benefits outweigh the risks. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when tacrolimus and other protease inhibitors (e.g., ritonavir) are used concomitantly.

Antifungal Agents

Frequent monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when concomitant use of the following antifungal drugs with tacrolimus is initiated or discontinued.

Azoles: Voriconazole, posaconazole, itraconazole, ketoconazole, fluconazole and clotrimazole inhibit CYP3A metabolism of tacrolimus and increase tacrolimus whole blood concentrations. When initiating therapy with voriconazole or posaconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be initially reduced to one-third of the original dose and the subsequent tacrolimus doses be adjusted based on the tacrolimus whole blood concentrations.

Caspofungin is an inducer of CYP3A and decreases whole blood concentrations of tacrolimus.

Calcium Channel Blockers

Verapamil, diltiazem, nifedipine, and nicardipine inhibit CYP3A metabolism of tacrolimus and may increase tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these calcium channel blocking drugs and tacrolimus are used concomitantly.

Antibacterials

Erythromycin, clarithromycin, troleandomycin and chloramphenicol inhibit CYP3A metabolism of tacrolimus and may increase tacrolimus whole blood concentrations. Monitoring of blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly**.**

Antimycobacterials

Rifampin and rifabutin are inducers of CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these anti-mycobacterial drugs and tacrolimus are used concomitantly.

Anticonvulsants

Phenytoin, carbamazepine and phenobarbital induce CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.

Concomitant administration of phenytoin with tacrolimus may also increase phenytoin plasma concentrations. Thus, frequent monitoring phenytoin plasma concentrations and adjusting the

phenytoin dose as needed are recommended when tacrolimus and phenytoin are administered concomitantly.

St. John's Wort (*Hypericum perforatum*)

St. John's Wort induces CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when St. John's Wort and tacrolimus are co-administered.

Gastric Acid Suppressors/Neutralizers

Lansoprazole and omeprazole, as CYP2C19 and CYP3A4 substrates, may potentially inhibit the CYP3A4 metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers.

Cimetidine may also inhibit the CYP3A4 metabolism of tacrolimus and thereby substantially increase tacrolimus whole

blood concentrations. Coadministration with magnesium and aluminum hydroxide antacids increase tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.

Others

Bromocriptine, nefazodone, metoclopramide, danazol, ethinyl estradiol and methylprednisolone may inhibit CYP3A metabolism of tacrolimus and increase tacrolimus whole blood concentrations. Monitoring of blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are co-administered.

USE IN SPECIAL POPULATION

Pregnancy Category C

Tacrolimus should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus

Lactation

Tacrolimus is excreted in human milk. As the effect of chronic exposure to tacrolimus in healthy infants is not established, patients maintained on tacrolimus should discontinue nursing taking into consideration importance of drug to the mother.

Pediatric use:

The safety and efficacy of tacrolimus in pediatric kidney and heart transplant patients have not been established. Successful liver transplants have been performed in pediatric patients (ages up to 16 years) using tacrolimus.

Geriatric use

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic impairment

The mean clearance of tacrolimus was substantially lower in patients with severe hepatic impairment (mean Child-Pugh score: >10) compared to healthy volunteers with normal hepatic function. Close monitoring of tacrolimus trough concentrations is warranted in patients with hepatic impairment.

Renal impairment

Consideration should be given to dose tacrolimus at the lower end of the therapeutic dosing range in patients who have received a liver or heart transplant and have pre-existing renal impairment. Further reductions in dose below the targeted range may be required

OVERDOSAGE

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 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 over dosage.

STORAGE

Store Protected from moisture at a temperature not exceeding 30^0c.

PRESENTATION

Tacrolimus Capsules IP 0.5 mg – 6 X 10 Capsules
Tacrolimus Capsules IP 1 mg – 6 X 10 Capsules
Tacrolimus Capsules IP 5 mg – 1 X 10 Capsules