FIRST FOLD SHOULD BE HORIZONTAL & REMAINING VERTICAL

TRANSGRAF CAPSULE

(Tacrolimus Capsules USP 0.5/1/5 mg)

NAME AND STRENGTH OF ACTIVE SUBSTANCE
Tacrolimus Monohydrate

COMPOSITION:
1.Transgraf capsule 0.5 mg
Each Hard gelatin capsule contains :
Tacrolimus USP (as Monohydrate) equivalent to Tacrolimus.....0.5mg
Colour : Titanium Dioxide and Yellow Iron Oxide
2.Transgraf capsule 1 mg
Each hard gelatin capsule contains :
Tacrolius USP (as Monohydrate) equivalent to Tacrolimus.....1mg
Colour : Titanium Dioxide
3.Transgraf capsules 5 mg
Each hard gelatin capsule contains :
Tacrolimus USP (as Monohydrate) equivalent to Tacrolimus.....5mg
Colour : Titanium Dioxide, Red iron oxide

PRODUCT DESCRIPTION
Transgraf capsule 0.5 mg
White to off white powder filled in size "5" yellow coloured cap/yellow coloured body hard gelatin capsules printed with "0.5 mg" on cap and "Tacro" on body with red ink.
Transgraf capsule 1 mg
White to off white powder filled in size "5" white coloured cap/white coloured body hard gelatin capsules printed with "1 mg" on cap and "Tacro" on body with red ink.
Transgraf capsules 5 mg
White to off white powder filled in size "4" greyish red coloured cap/greyish red coloured body hard gelatin capsules printed with "5 mg" on cap and "Tacro" on body with white ink.

PHARMACODYNAMICS
Pharmacotherapeutic group: Calcineurin inhibitors, ATC code: L04AD02

Mechanism of action and pharmacodynamic effects
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.

PHARMACOKINETICS
Absorption
Tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Peak concentrations (Cmax) of tacrolimus in blood are achieved in approximately 1 - 3 hours following oral administration. The mean oral bioavailability of tacrolimus is in the range of 20% - 25%.
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.
Bile flow does not influence the absorption of tacrolimus.
A strong correlation exists between AUC and whole blood trough levels at steady-state. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

Distribution and elimination
In man, the disposition of tacrolimus after intravenous infusion may be described as biphasic.
In the systemic circulation, tacrolimus binds strongly to erythrocytes resulting in an approximate 20:1 distribution ratio of whole blood/plasma concentrations. In plasma, tacrolimus is highly bound (> 98.8%) to plasma proteins, mainly to serum albumin and α-1-acid glycoprotein.
Tacrolimus is extensively distributed in the body.
Tacrolimus is a low-clearance substance. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of tacrolimus, or corticosteroid-induced increased metabolism are considered to be responsible for the higher clearance rates observed following transplantation. The half-life of tacrolimus is long and variable. In normal patient, the mean half-life in whole blood is approximately 43 hours. Increased clearance rates contribute to the shorter half-life observed in transplant recipients.

Metabolism and biotransformation
Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4. Tacrolimus is also considerably metabolised in the intestinal wall. There are several metabolites identified. 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
Tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination

INDICATIONS AND USAGE
Primary immunosuppression in liver and kidney allograft recipients and liver and kidney allograft rejection resistant to conventional immunosuppressive agents. It is recommended that Tacrolimus be used concomitantly with adrenal corticosteroids.

DOSAGE AND ADMINISTRATION
Route of administration
Oral

Recommended Dose
Tacrolimus therapy requires careful monitoring by adequately qualified and equipped personnel. The medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients.
The dosage recommendations given below for oral and intravenous administration are intended to act as a guideline. Tacrolimus doses should be adjusted according to individual patient requirements.
Dosing should commence orally, if necessary via an intranasal gastric tube. If the clinical condition of the patient does not allow oral therapy, initial intravenous dosing may be necessary.

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

Primary immunosuppression dose levels – Paediatric patients
Paediatric patients generally require doses 1.5 to 2 times higher than the recommended adult doses to achieve the same blood levels.

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

Maintenance Therapy Dose Levels
It is necessary to continue immunosuppression with oral Tacrolimus to maintain graft survival. Dose can frequently be reduced during maintenance therapy. Dosing should be primarily based on clinical assessments of rejection and tolerability of the patient.
If progression of disease occurs (eg. Signs of acute rejection) alteration of the immunosuppressive regimen should be considered. Increase the amount of corticosteroids, introduction of short courses of mono/polyclonal antibodies and increase in the dose of Tacrolimus have been used to manage rejection episodes.
If signs of toxicity (eg. Pronounced adverse event) are noted, the dose of Tacrolimus should be reduced.
When Tacrolimus is administered in combination with a corticosteroid these may often be reduced and in rare cases the treatment has continued as monotherapy.

Therapy dose levels for liver and kidney allograft rejection resistant to conventional immunsuppressive regimens.
In patients experiencing rejections episodes which are unresponsive to conventional immunosuppressive therapy, Tacrolimus treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.
Care should be taken when converting patients from ciclosporin-based to Tacrolimus-based therapy. Tacrolimus should be initiated after considering cyclosporin blood concentrations and the clinical condition of the patient. In practice, Tacrolimu therapy has been initiated 12 – 24 hours after discontinuation of cyclosporine. Monitoring of cyclosporine blood levels should be continued following conversion as the clearance of cyclosporin may be affected.

Patient with liver impairment
A dose reduction is necessary.

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

Elderly patients
Limited experience suggests that doses should be the same as for adults.

Duration of dosing
For oral dosing the capsules normally have to be taken continuously to suppress graft rejection and no limit for therapy duration can be given. Patients should be converted from intravenous to oral medication as soon as individual circumstances permit. Intravenous therapy should not be continued for more than 7 days.

CONTRAINDICATIONS
Tacrolimus capsules are contraindicated in following condition :
- Hypersensitivity to tacrolimus or other macrolides.
- Hypersensitivity to any of the excipients.

WARNING AND PRECAUTIONS
During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.
Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate or prolonged release tacrolimus formulations, have been observed. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under or overexposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist.
Herbal preparations containing St. John's wort (Hypericum perforatum) or other herbal preparations should be avoided when taking Tacrolimus due to the risk of interactions that lead to decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus.
Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea.
The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin.
Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed on rare occasions. Most cases have been reversible, occurring primarily in children with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high risk patients, particularly young children and those receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre and post transplant (e.g. initially at three months and then at 9-12 months). If abnormalities develop, dose reduction of Tacrolimus therapy, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval and may cause Torsades de Pointes. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heartfailure, bradyarrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure
Patients treated with Tacrolimus have been reported to develop EBV associated lymphoproliferative disorders. Patients switched to Tacrolimus therapy should not receive antilymphocyte treatment concomitantly. Very young (<2 years), EBV-VCA negative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA
Serology should be ascertained before starting treatment with Tacrolimus. During treatment, careful monitoring with EBV-PCR is recommended.Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma.
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.
Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppressants. These infections may lead to serious, including fatal outcomes. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus.
All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA.
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.
As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown.
As Transgraf contains lactose, special care should be taken in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption.

INTERACTIONS WITH OTHER MEDICAMENTS
Metabolic interactions
Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is therefore recommended to monitor tacrolimus blood levels whenever substances which have the potential to alter CYP3A metabolism are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure.

Inhibitors of metabolism
Clinically the following substances have been shown to increase tacrolimus blood levels:
Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin or HIV protease inhibitors (e.g. ritonavir). Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients.
Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, danazol, ethinylestradiol, omeprazole and nefazodone.
In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen, troleandomycin. Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.
Lansoprazole and ciclosporin may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

Inducers of metabolism
Clinically the following substances have been shown to decrease tacrolimus blood levels:
Strong interactions have been observed with rifampicin, phenytoin or St. John's Wort (Hypericum perforatum) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.
High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels.
Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

Effect of tacrolimus on the metabolism of other medicinal products
Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolised by CYP3A4 may affect the metabolism of such medicinal products.
The half-life of ciclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can

occur. For these reasons, the combined administration of ciclosporin and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin.
Tacrolimus has been shown to increase the blood level of phenytoin.
As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures.
Limited knowledge of interactions between tacrolimus and statins is available. Available data suggests that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus.
Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and phenazone.

Other interactions which have led to clinically detrimental effects
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole+trimethoprim, NSAIDs, ganciclovir or aciclovir).
Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.
As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone) should be avoided.
Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

Protein binding considerations
Tacrolimus is extensively bound to plasma proteins. Possible interactions with other medicinal products known to have high affinity for plasma proteins should be considered (e.g., NSAIDs, oral anticoagulants, or oral antidiabetics).

PREGNANCY AND LACTATION
Pregnancy
Human data show that tacrolimus is able to cross the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. To date, no other relevant epidemiological data are available.
Due to the need of treatment, tacrolimus can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus. In case of in utero exposure, monitoring of the newborn for the potential adverse effects of tacrolimus is recommended (in particular the effects on the kidneys). There is a risk for premature delivery (<37 week) as well as for hyperkalaemia in the newborn, which, however, normalizes spontaneously.
In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity. Tacrolimus affected male fertility in rats.

Lactation
Human data demonstrate that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving tacrolimus

SIDE 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; common; uncommon; rare; very rare; not known

Infections and infestations
As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.
Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Tacrolimus.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Blood and lymphatic system disorders
common anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal
uncommon coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia
rare thrombotic thrombocytopenic purpura, hypoprothrombinaemia
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

Psychiatric disorders
very common Insomnia
common anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders
Uncommon psychotic disorder

Nervous system disorders
very common tremor, headache
common seizures, disturbances in consciousness, paraesthesias anddysaesthesias, 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 Hypertoniavery
Very rare myasthenia

Eye disorders
common vision blurred, photophobia, eye disorders uncommoncataract
rare blindness

Ear and labyrinth disorders
common tinnitus
Uncommon hypoacusis
rare deafness neurosensory
very rare hearing impaired

Cardiac disorders
common ischaemic coronary artery disorders, tachycardia
uncommon ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, abnormal ECG investigations, abnormal heart rate and pulse investigations
rare pericardial effusion
very rare Abnormal echocardiogram, prolonged ECG QT, 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, asthmarareacute 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 uncommondermatitis, photosensitivity
rare toxic epidermal necrolysis (Lyell's syndrome) very rareStevens Johnson syndrome

Musculoskeletal and connective tissue disorders
common arthralgia, muscle spasms, pain in limb, back pain uncommonjoint disorders

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 rarenephropathy, 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 disturbeduncommon multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal
rare thirst, fall, chest tightness, ulcer very rarefat tissue increased

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).

SYMPTOMS AND TREATMENT OF 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 ef fective 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if tacrolimus is administered in association with alcohol

SHELF LIFE
24 months from date of manufacturing

STORAGE CONDITION
Store below 30°C in dry place. Protect from light.

PRESENTATION
Each blister contains 10 capsules. Such 5 blisters are packed in trilaminated pouch with Silica Gel Packet. One or Two Trilaminated pouch is packed in outer carton along with pack insert.
Available pack size: 5 x 10's pouch pack
2 x 5 x 10's pouch pack

ALKEM
Manufactured by:
ALKEM LABORATORIES LTD.
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