Biocon

Tacrolimus Capsules

TACROGRAF™ - 0.25/0.5/1/2/3/5 टैक्रोग्राफ़ -०.२५/०.५/१/२/३/५

Composition
TACROGRAF™ - 0.25
Each hard gelatin capsule contains: Tacrolimus 0.25 mg
TACROGRAF™ - 0.5
Each hard gelatin capsule contains: Tacrolimus 0.5 mg
TACROGRAF™ - 1
Each hard gelatin capsule contains: Tacrolimus 1 mg
TACROGRAF™ - 2
Each hard gelatin capsule contains: Tacrolimus 2 mg
TACROGRAF™ - 3
Each hard gelatin capsule contains: Tacrolimus 3 mg
TACROGRAF™ - 5
Each hard gelatin capsule contains: Tacrolimus 5 mg

Description
Tacrolimus is a 23-membered macrolide lactone. It is an immunosuppressive drug whose main use is after allogenic organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}.H_2O$ and a formula weight of 822.03.

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 and Distribution
Tacrolimus is rapidly, albeit incompletely, absorbed in the gastrointestinal tract, with peak tacrolimus concentrations in whole-blood (Cmax) attained approximately1-2 hours after oral administration. In renal and liver transplant recipients receiving oral tacrolimus 0.3 mg/kg/day, respective Cmax values were 24.2 and 68.5 ng/mL, with corresponding AUC values of 288 and 519 ng. h/mL.
The oral bioavailability of tacrolimus is poor, with an average bioavailability of 25% (range 4-93%) The relatively low bioavailability of the drug most likely reflects incomplete absorption in the GI tract and/or gut metabolism of tacrolimus. Mean oral bioavailability of tacrolimus was similar between adult (25%) and paediatric (31%) transplant recipients.
The rate and extent of absorption of tacrolimus is reduced in the presence of food. In healthy volunteers and liver transplant recipients, Cmax decreased in relation to the fasting state by approximately 50-75% and AUC by 25-40% when the drug was taken after a meal, with this effect more marked in those receiving a high fat meal. Tacrolimus is highly bound to erythrocytes, with blood : plasma ratios showing wide variability. Plasma protein binding may be as high as 99%, with the majority of the drug bound to µ1-acid glycoprotein and albumin.
Animal studies indicate tacrolimus is widely distributed into most tissues including the lungs, spleen, heart, kidney, pancreas, brain, muscle and liver. Tacrolimus crosses the placenta, with umbilical cord plasma concentrations approximately one-third of those in maternal plasma. In addition, levels in breast milk were reported to be similar to those observed in the plasma.

Metabolism and Elimination
Tacrolimus undergoes extensive metabolism in the liver, with less than 1% of unchanged drug excreted in the urine. Although hepatic metabolism predominates, the drug is also metabolised to a much lesser extent in the intestinal mucosa, with metabolism mediated at both sites by cytochrome P450 (CYP) 3A4 isoenzymes.P-glycoprotein is also involved in metabolism in the intestinal mucosa. Tacrolimus is converted by hydroxylation and demethylation to at least 15 metabolites, with the main metabolite being 13-*O*-demethyl-tacrolimus. While the parent drug is primarily responsible for the immunosuppressive activity, 13-*O*-demethyl-tacrolimus also shows some activity as may some of the other metabolites. The mean terminal elimination half-life (t1/2) in adult renal or liver transplant recipients was approximately 19 and 12 hours,

Special patient population
Children
Children typically require higher tacrolimus dosages on a milligram per kilogram basis than adult patients, most likely reflecting the higher CL (0.138 vs 0.06 L/h/kg) and Vd (2.6 vs 1 L/kg) values in children than adults.

Renal impairement
Patients with severe renal dysfunction (serum creatinine levels ranging from 344-1061 µmol/L) prior to renal transplantation had similar tacrolimus clearance values to those reported in healthy volunteers (0.038 vs 0.040 L/h/kg).

Hepatic impairement
Although there was no difference in mean CL values between adult patients with mild hepatic impairment (mean Child Pugh score 6.2) and healthy adult volunteers, in adult patients with severe hepatic impairment (mean Child Pugh score >10) there were marked differences in CL relative to healthy adult 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.

Indications
Tacrolimus is indicated for the prophylaxis of organ rejection in patients receiving organ transplant.

Contraindications
Tacrolimus is contraindicated in patients with a hypersensitivity to tacrolimus or any component of the drug product.

Warnings
Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of tacrolimus treated kidney transplant patients without pretransplant history of diabetes millitus in clinical studies. Insulin dependence was reversible in 15% of these PTDM patients at one year and in 50% at two years post transplant.
Tacrolimus can cause nephrotoxicity, particularly when used in high doses. 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.
Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients treated with tacrolimus in randomized trials. Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during Tacrolimus therapy.
Neurotoxicity, including tremor, headache, and other changes in motor function, mental status, and sensory function were reported in approximately 54% in tacrolimus treated kidney transplant patients compared to cyclosporine-treated patients. Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment. Seizures have occurred in adult and pediatric patients receiving tacrolimus. Coma and delirium also have been associated with high plasma concentrations of tacrolimus.
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.

Precautions
General
Tacrolimus therapy can cause mild or moderate hypertension and 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.

Renal & Hepatic impaired patients
For patients with renal & hepatic impairement some evidence suggests that lower doses should be used.

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. 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.

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Carcinogenesis, Mutagenesis and Impairment of Fertility
An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphomas and carcinomas of the skin.As with other immunosuppressive therapies, the risk of malignancies in Tacrolimus recipients may be higher than in the normal, healthy population. Lymphoproliferative disorders associated with Epstein-Barr Virus infection have been seen. It has been reported that reduction or discontinuation of immunosuppression may cause the lesions to regress.

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. Carcinogenicity studies were carried out in male and female rats and mice.In the 80-week mouse study and in the 104-week rat study no relationship of tumor incidence to tacrolimus dosage was found. No impairment of fertility was demonstrated in studies of male and female rats.

Pregnancy: Category C
In reproduction studies in rats and rabbits, adverse effects on the fetus were observed mainly at dose levels that were toxic to dams. Tacrolimus at oral doses of 0.32 and 1.0 mg/kg during organogenesis in rabbits was associated with maternal toxicity as well as an increase in incidence of abortions; these doses are equivalent to 0.5 1X and 1.6 3.3X the recommended clinical dose range (0.1 0.2 mg/kg) based on body surface area corrections. At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg (equivalent to 0.7 1.4X and 2.3 4.6X the recommended clinical dose range based on body surface area corrections) to pregnant rats after organogenesis and during lactation, was associated with reduced pup weights. No reduction in male or female fertility was evident.
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.

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

Pediatric Patients
Experience with tacrolimus in pediatric kidney and heart transplant patients is limited. Successful liver transplants have been performed in pediatric patients (ages up to 16 years) using Tacrolimus. Two randomized active-controlled trials of tacrolimus in primary liver transplantation included 56 pediatric patients. Thirty-one patients were randomized to Tacrolimus-based and 25 to cyclosporine-based therapies. Additionally, a minimum of 122 pediatric patients were studied in an uncontrolled trial of tacrolimus in living related donor liver transplantation. Pediatric patients generally required higher doses of Tacrolimus to maintain blood trough concentrations of tacrolimus similar to adult patients

Drug interactions
Tacrolimus is extensively metabolised in the liver and intestinal mucosa by CYP3A4 isoenzymes and P-glycoprotein and thus, drugs interacting with these systems may affect the pharmacokinetic properties of tacrolimus.
The main CYP3A4 inhibitors that may potentially increase whole-blood tacrolimus concentrations are various calcium antagonists (diltiazem, nicardipine, nifedipine and verapamil), Imidazole antifungal agents (clotrimazole, fluconazole, itraconazole and ketoconazole), macrolide antibacterial agents (clarithromycin and erythromycin), prokinetic agents (cisapride and metoclopramide), other drugs like bromocriptine, cimetidine, corticosteroids, cyclosporin, danazol ethinyl estradiol, omeprazole, lansoprazole nefazodone, magnesium aluminum hydroxide, protease inhibitors and grapefruit juice.
Enzyme inducers that may decrease tacrolimus concentrations include certain anticonvulsants (carbamazepine, phenobarbital and phenytoin), as well as rifabutin and rifampicin. Similarly, concomitant administration with St. John's wort reduced whole-blood concentrations of tacrolimus and increased clearance of the drug most likely mediated via induction of CYP3A4 and P-glycoprotein.
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

Side effects
Most Frequent:
Abdominal pain with cramps, anemia, anorexia, anxiety, blood dyscrasias, CNS toxicity, constipation, depression, diarrhea, dizziness, erythroblastic anemia, feeling agitated, gastrointestinal Irritation, general weakness, hallucinations, headache, hperglycemia, hyperkalemia, hypomagnesemia, impaired cognition, infection, insomnia, leukopenia, nausea, nephrotoxicity, nervousness, nightmares, paresthesia, peripheral edema, pleural effusions, pruritus, seizures, skin rash, tremors, vomiting

Less Frequent:
Cardiomyopathy, chest pain, cramps, hyperhidrosis, hyperlipidemia, hypertension, hypertriglyceridemia, neuropathy, osteoporosis, tinnitus, visual changes

Rare:
Acute pancreatitis, conduction disorder of the heart, drug-induced hepatitis, gastric ulcer, gastroenteritis, glycosuria, hearing loss, hemolytic uremic syndrome, idiopathic thrombocytopenic purpura, left ventricular hypertrophy, leukoencephalopathy, post transplant lymphoproliferative disease, prolonged QT interval, renal failure, Stevens-Johnson Syndrome, torsades de pointes

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. Occasionally, acute overdosage has been followed by adverse reactions consistent with those listed in the **ADVERSE REACTIONS** section except in one case where 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

Dosage & Administration
Kidney Transplantation
The recommended starting oral dose of Tacrolimus is 0.2 mg/kg/day administered every 12 hours in two divided doses. The initial dose of tacrolimus may be administered within 24 hours of transplantation. Some patients may require higher doses to achieve comparable blood concentrations.

Patients with Hepatic or Renal Dysfunction
Due to the potential for nephrotoxicity, patients with renal or hepatic impairment should receive doses at the lowest value of the recommended oral dosing ranges. Further reductions in dose below these ranges may be required. Tacrolimus therapy usually should be delayed up to 48 hours or longer in patients with post-operative oliguria.

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 posttransplant time. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies. During the first three months, 80% of the patients maintained trough concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through 1 year.
The relative risk of toxicity is increased with higher trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity.

Storage:
Store in a cool, dry place protect from moisture. Keep the medicine out of reach of children.

Presentation:
TACROGRAF™ 0.25 - available as 10 capsules per unit pack
TACROGRAF™ 0.5 - available as 10 capsules per unit pack
TACROGRAF™ 1 - available as 10 capsules per unit pack
TACROGRAF™ 2 - available as 10 capsules per unit pack
TACROGRAF™ 3 - available as 10 capsules per unit pack
TACROGRAF™ 5 - available as 10 capsules per unit pack

For further information, please contact:
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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No: **1800 102 9465** or e mail us at **drugsafety@biocon.com**

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