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## Drug Profile

### TACROLIMUS

Tacrolimus is a macrolide lactone with potent immuno suppressive activity, isolated from streptomyces tsukubaensis. In contrast to all other US food & Drug Administration (FDA) approved immuno-suppressive agents developed to date, the clinical development of tacrolimus was conducted primarily in liver transplantation in 1994. It was used in Renal transplant recipients in 1996. It is viewed widely as preferable to cyclosporine for maintenance immuno suppression in high-immunological risk renal allograft recipients (Repeat renal transplant recipients, high panel reactive antibody renal transplant recipients, & combined kidney-pancreas transplant recipients). More recent experiences indicated that tacrolimus may have additional properties, including steroid-sparing properties, that may be superior to cyclosporine.

**Mechanism of action :** It exerts potent inhibitory effect on T-Lymphocyte activation. It binds to immunophilins FK 506 binding proteins (FKBP-12) and a complex of FKBP-12, Calcium, calmodulin & Calcineurin is formed, inhibiting phosphatase activity of calcineurin. This prevents dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT) and inhibits transcription of early T-cell activation gene, interleukin-2, Tumor necrosis factor (TNF- $\alpha$ ) and proto-oncogenes; suppressing expression of IL-2 and IL-7 receptor. This results in inhibition of T-Lymphocyte activation. Tacrolimus also inhibits the mixed lymphocyte reaction, generation of cytotoxic T-cells dependent B-Cell activation.

**Pharmacokinetics :** Absorption of Tacrolimus after oral administration is incomplete & variable with oral bioavailability of 4-93% and mean bioavailability of 25%. Food appears to reduce the absorption & relative bioavailability of tacrolimus. In most cases, CMax is achieved after 0.5 to 1 hour. It is mainly metabolized (799%) in liver by a cytochrome isoenzyme (P450 CYP3A) to at least 15 compounds. The main route of elimination of tacrolimus metabolites is biliary & less than it is excreted unchanged in urine. Fecal elimination is around 92%.

**Indication & Usage :** It is used in liver & kidney transplant cases as immuno suppressive drug.

**Warning:** Administration of tacrolimus may cause diabetes mellitus. Neurotoxicity & nephrotoxicity. Mild to moderate hyper kalemia may occur with it. Patients receiving tacrolimus are at high risk of lymphomas, malignancies & infections due to oversuppression of immune system. Mild to moderate hyper-

tension is common with the drug.

**Precautions :** Patients with hepatic & renal impairment, lower dosage should be used.

Hypertrophic cardiomyopathy - It is observed in infant & children. Dosage reduction or discontinuation of therapy is required.

Pregnancy - No well controlled trials. It should be used only if the benefits outweigh potential risk to fetus.

Nursing mothers - Since it is excreted in human milk, should be avoided in nursing mothers.

**Drug Interaction:** As tacrolimus is metabolized by cytochrome P450 CYP3A enzyme, potential drug interactions are -

(a) increased tacrolimus blood concentration - Calcium channel blockers antifungal agents, macrolide antibiotics, corticosteroids, cyclosporine, prokinetic drugs, omeprazole & bromocriptine. (b) Decreased Tacrolimus blood concentration - Anticonvulsant, anticoagulants antacids & rifampicin. Vaccines - Drug may reduce the efficacy of vaccines & recipients of tacrolimus should not receive live attenuated vaccines.

**Adverse Reactions :** Tacrolimus shows adverse events common to other immuno suppressive therapies viz, neurotoxicity, nephrotoxicity, increased risk of infections & malignancy, diabetes mellitus & a lymphoproliferative disorder, related to Epstein Barr Virus common adverse events are - Nervous System - Tremor, headache, paresthesia, dizziness, insomnia, seizures, GI Tract - Diarrhoea, constipation, Nausea, vomiting, dyspepsia. CUS - hypertension chest pain.

**Metabolic Disturbance** - Hyperkalemia, hyper chloremic acidosis, hypomagnesemia - diabetes mellitus, hypercholesterolemia. Hypertension, Nephrotoxicity- Reduced Renal blood flow, glomerular perfusion, tubular & vascular toxicity.

**Dosage & Administration** - dosage 0.2mg/kg/day in 2 divided doses. The target trough blood levels of tacrolimus is 12-15 ng/ml in 1st month post transplant period, 1-3 months after transplant 10-12 ng/ml, 5-10ng/ml 3-6 month after transplant.