HOSPIMAX
Maximising Life

FujiGraf®

Tacrolimus 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg Capsules

Better Graft Survival, Minimal Rejection

Product Description:

- Fujigraf 0.25: Each hard gelatin capsule contains Tacrolimus USP 0.25 mg
- Fujigraf 0.5: Each hard gelatin capsule contains Tacrolimus USP 0.5 mg
- Fujigraf 1: Each hard gelatin capsule contains Tacrolimus USP 1 mg
- Fujigraf 2: Each hard gelatin capsule contains Tacrolimus USP 2 mg

General Information

Tacrolimus, also known as fujimycin is an immunosuppressive drugused mainly after allogeneic organ transplant to reduce the risk of organ rejection. It inhibits the production of interleukin-2, a molecule that promotes the development and proliferation of T cells, which are mainly responsible for body's immune response.

Tacrolimus is a macrolide isolated from the fermentation broth of a strain of Streptomyces tsukubaensis that has strong immunosuppressive activity through prevention of the activation of T-lymphocytes

Indication & Usage

1- **Prophylaxis of Organ Rejection in Kidney Transplant Patients.**
It is recommended that Fujigraf be used concomitantly with azathioprine or mycophenolate mofetil (MMF) and adrenal corticosteroids.Therapeutic drug monitoring is recommended for all patients receiving Fujigraf.

2- **Prophylaxis of Organ Rejection in Liver Transplant Patients.**
It is recommended that Fujigraf be used concomitantly with adrenal corticosteroids. Therapeutic drug monitoring is recommended for all patients receiving Fujigraf.

3- **Prophylaxis of Organ Rejection in Heart Transplant Patients**
It is recommended that Fujigrafbe used concomitantly with azathioprine or mycophenolate mofetil (MMF) and adrenal corticosteroids. Therapeutic drug monitoring is recommended for all patients receiving Fujigraf

DOSAGE AND ADMINISTRATION

- **Adult kidney transplant patients:**
    - In combination with Azathioprine: 0.2 mg/kg/day in two divided doses, every 12 hour

  - In combination with MMF/ IL-2 receptor antagonist: 0.1 mg/kg/day in two divided doses, every 12 hour
- **Adult liver transplant patients**:
  - 0.10-0.15 mg/kg/day in two divided doses, every 12 hour
- **Adult heart transplant patients**:
  - 0.075 mg/kg/day in two divided doses, every 12 hour
- **Pediatric liver transplant patients**:
  - 0.15-0.20 mg/kg/day in two divided doses, every 12 hour

Mechanism of action

Tacrolimus is a calcineurin inhibitor.Tacrolimus inhibits T-lymphocyte activation by first binding to an intracellular protein, FKBP-12. This FKBP12–Tacrolimus complex interacts with and inhibits calcineurin, thus inhibiting both T-lymphocyte signal transduction and IL-2 transcription. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited.

Pharmacokinetic

Absorption: Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. The absolute bioavailability in adult kidney transplant patients is 17±10%; in adults liver transplant patients is 22±6%; in healthy subjects is 18±5%.

The rate of tacrolimus absorption is higher in fasting condition.The rate of absorption of tacrolimus decreased after taking food.

Fujigraf can be taken with or without food everyday as presence and composition of food reduces the bioavailability of Fujigraf

Distribution:

The plasma protein binding of tacrolimus is 99% over a concentration range of 5-50 ng/ml. Tacrolimus primarily bound to albumin and alpha-1 acid glycoprotein. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as haematocrit, temperature at the time of plasma separation, drug concentration and plasma protein concentration

Metabolism:

Tacrolimus is metabolized by the mixed function oxidase system, mainly the cytochrome P-450 system(CYP3A). 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

In men, less than 1% of the dose administered is excreted unchanged in urine. After oral administration, fecal elimination is found to be 92.6 ± 30.7%, urinary elimination 2.3 ± 1.1% and the elimination half-life based on radioactivity is 31.9 ± 10.5 hours whereas it is 48.4 ± 12.3 hours based on Tacrolimus concentrations.

Use in Specific Population

Pregnancy: Tacrolimus can cause fetal harm when administered to pregnant women.

Lactation: Controlled lactation studies have not been conducted in humans, however tacrolimus has been reported to be present in human milk. The effects of tacrolimus on breastfed infant, or on milk production have not been assessed

Pediatric Use: Safety & effectiveness have been established in pediatric liver, kidney and heart transplant patient

Geriatic Use: Dose selection for an eldery patients 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

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

Warning & Precaution:

Lymphoma & other malignancies: Patients receiving tacrolimus are at high risk of developing lymphomas & other malignancies, particularly of skin

Serious Infection: Patients receiving tacrolimus are at high risk of developing various infection like viral, bacterial, fungal and protozoal infections

New Onset of Diabetes After Transplant: Patients on tacrolimus may develop new onset of diabetes after kidney, liver & heart transplantation. Blood glucose concentration to be monitored closely in patients using tacrolimus

Adverse Reactions:

- Various adverse reaction related to tacrolimus are as follows
- Lymphoma & other malignancies
- Serious Infections
- New Onset of Diabetes After Transplant:
- Nephrotoxicity
- Neurotoxicity

- Hyperkalemia
- Hypertension
- Myocardial Hypertrophy
- Pure red cell aplasia

Therapeutic Drug Monitoring

Tacrolimus blood concentration monitoring is considered to be an essential part of patient management for prevention of rejection, toxicity, dose adjustment and compliance

Below mentioned is the whole blood trough concentration range of different patients group which is to be taken into consideration while administering tacrolimus to patients

Type of Patients	**Blood trough concentration range**
Kidney Transplant Patients	
With Azathioprine	Month 1-3: 7-20 ng/ml Month 4-12: 5-15 ng/ml
With MMF/IL-2 receptor antagonist	Month 1-12: 4-11 ng/ml
Liver Transplant Patients	
With corticosteroids only	Month 1-12: 5-20 ng/ml
Heart Transplant Patients	
With Azathioprine or MMF	Month 1-3: 10-20 ng/ml Month ≥ 4: 5 -15 ng/ml