Tacrograf
Tacrolimus

COMPOSITION
Tacrograf 0.5 Capsule: Each capsule contains Tacrolimus Monohydrate USP equivalent to Tacrolimus 0.5 mg
Tacrograf 1 Capsule: Each capsule contains Tacrolimus Monohydrate USP equivalent to Tacrolimus 1 mg

PHARMACOLOGY
Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (a ubiquitous mammalian intracellular enzyme) is then formed, after which the phosphatase activity of calcineurin is inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT), and nuclear factor kappa-light-chain enhancer of activated B-cells (NF-κB).
Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony-stimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation, as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

INDICATIONS
Tacrolimus is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic liver, kidney, heart, or lung transplants, in combination with other immunosuppressants.

DOSAGE AND ADMINISTRATION
If patients are able to tolerate oral therapy, the recommended oral starting doses should be initiated.
- The initial dose of Tacrolimus capsules should be administered no sooner than 6 hours after transplantation in the liver, heart, or lung transplant patients.
- In kidney transplant patients, the initial dose of Tacrolimus capsules may be administered within 24 hours of transplantation but should be delayed until renal function has recovered.

Initial Oral Tacrolimus Capsules Dosage Recommendations and Whole Blood Trough Concentration Range in Adults:

Patient Population	Tacrolimus Capsules Initial Oral Dosage Note: Daily doses should be administered as two divided doses, every 12 hours	Whole Blood Trough Concentration Range
Adult kidney transplant patients: In combination with azathioprine In combination with MMF/IL-2 receptor antagonist	 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: With corticosteroids only	0.10-0.15 mg/kg/day	month 1-12: 5-20 ng/mL
Adult heart transplant patients: With azathioprine or MMF	0.075 mg/kg/day	month 1-3: 10-20 ng/mL month ≥4: 5-15 ng/mL
Adult Lung Transplant patients: With azathioprine or MMF	0.075 mg/kg/day	Month 1-3: 10-15 ng/mL Month 4-12: 8-12 ng/mL

Note: In lung transplantation, cystic fibrosis patients may have a reduced bioavailability of orally administered tacrolimus resulting in the need for higher doses to achieve target tacrolimus trough concentrations. Monitor tacrolimus trough concentrations and adjust the dose accordingly.

Initial Oral Tacrolimus Capsules Dosage Recommendations and Whole Blood Trough Concentration Range in Childrens:

Patient Population	Tacrolimus Capsules Initial Oral Dosage Note: Daily doses should be administered as two divided doses, every 12 hours	Whole Blood Trough Concentration Range
Pediatric kidney transplant patients	0.3 mg/kg/day	Month 1-12: 5-20 ng/mL
Pediatric liver transplant patients	0.15-0.2 mg/kg/day	Month 1-12: 5-20 ng/mL
Pediatric heart transplant patients	0.3 mg/kg/day	Month 1-12: 5-20 ng/mL
Pediatric lung transplant patients	0.3 mg/kg/day	Week 1-2: 10-20 ng/mL Week 2 to Month 12: 10-15 ng/mL

Note: In lung transplantation, cystic fibrosis patients may have a reduced bioavailability of orally administered tacrolimus resulting in the need for higher doses to achieve target tacrolimus trough concentrations. Monitor tacrolimus trough concentrations and adjust the dose accordingly.

CONTRAINDICATION
Hypersensitivity to tacrolimus or HCO-60 (polyoxyl 60 hydrogenated castor oil).

WARNINGS AND PRECAUTIONS
- Not Interchangeable with Extended-Release Tacrolimus Products - Medication Errors: Instruct patients or caregivers to recognize the appearance of Tacrolimus capsules.
- New Onset Diabetes After Transplant: Monitor blood glucose.
- Nephrotoxicity (acute and/or chronic): Reduce the dose; use caution with other nephrotoxic drugs.
- Neurotoxicity: Including risk of Posterior Reversible Encephalopathy Syndrome (PRES); monitor for neurologic abnormalities; reduce or discontinue Tacrolimus.
- Hyperkalemia: Monitor serum potassium levels. Consider carefully before using with other agents also associated with hyperkalemia.
- Hypertension: May require antihypertensive therapy. Monitor relevant drug-drug interactions.
- Anaphylactic Reactions with IV formulation: Observe patients receiving Tacrolimus injection for signs and symptoms of anaphylaxis.
- Not recommended for use with sirolimus: Not recommended in liver and heart transplant due to increased risk of serious adverse reactions.
- Myocardial Hypertrophy: Consider dose reduction/discontinuation.
- Immunizations: Avoid live vaccines.
- Pure Red Cell Aplasia: Consider discontinuation of Tacrolimus.
- Thrombotic Microangiopathy, Including Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura: May occur, especially in patients with infections and certain concomitant medications.

SIDE EFFECTS
The most common adverse reactions (≥ 15%) were abnormal renal function, hypertension, diabetes mellitus, fever, CMV infection, tremor, hyperglycemia, leukopenia, infection, anemia, bronchitis, pericardial effusion, urinary tract infection, constipation, diarrhea, headache, abdominal pain, insomnia, paresthesia, peripheral edema, nausea, hyperkalemia, hypomagnesemia, and hyperlipemia.

USE IN SPECIFIC POPULATIONS
Pregnancy: Can cause fetal harm. Advise pregnant women of the potential risk to the fetus.

DRUG INTERACTIONS
- Mycophenolic Acid Products: Can increase MPA exposure after crossover from cyclosporine to Tacrolimus; monitor for MPA-related adverse reactions and adjust MMF or MPA dose as needed.
- Nelfinavir and Grapefruit Juice: Increased tacrolimus concentrations via CYP3A inhibition; avoid concomitant use.
- CYP3A Inhibitors: Increased tacrolimus concentrations; monitor concentrations and adjust tacrolimus dose as needed.
- CYP3A4 Inducers: Decreased tacrolimus concentrations; monitor concentrations and adjust tacrolimus dose as needed.
- Therapeutic drug monitoring and dose reduction for Tacrolimus should be considered when Tacrolimus is co-administered with cannabidiol.

OVERDOSAGE
Acute overdosages of up to 30 times the intended dose have been reported. Acute overdosage was sometimes followed by adverse reactions consistent with those reported with the use of Tacrolimus including tremors, abnormal renal function, hypertension, and peripheral edema. 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.

STORAGE
Store below 30° C, dry place, away from light and moisture. Keep out of the reach of children.

PACKAGING
Tacrograf 0.5 Capsule: Each commercial box contains 30 Capsules in Alu-Alu blister.
Tacrograf 1 Capsule: Each commercial box contains 30 Capsules in Alu-Alu blister.

Manufactured By
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