

## TACROLIMUS CAPS

**CLASS:** Calcineurin Inhibitor; Immunosuppressant Agent

**INDICATIONS: Organ rejection prophylaxis:**

*U.S. labeling:*

Astagraf XL: Prevention of organ rejection in kidney transplant recipients

Hecoria: Prevention of organ rejection in kidney and liver transplant recipients

Prograf: Prevention of organ rejection in heart, kidney, and liver transplant recipients

*Canadian labeling:*

Advagraf: Prevention of organ rejection in kidney transplant recipients

Prograf: Prevention of organ rejection in heart, kidney, or liver transplant recipients; treatment of refractory rejection in kidney or liver transplant recipients; treatment of active rheumatoid arthritis in adult patients nonresponsive to disease-modifying antirheumatic drug (DMARD) therapy or when DMARD therapy is inappropriate

### AVAILABLE DOSAGE FROM THE HOSPITAL:

TACROLIMUS 0.5MG CAP

TACROLIMUS 1MG CAP

TACROLIMUS 1MG CAP

### DOSAGE:

**-Prevention of organ rejection in transplant recipients: Note:** The initial postoperative dose of tacrolimus (immediate release) should begin no sooner than 6 hours after liver and heart transplant and within 24 hours of kidney transplant (but may be delayed until renal function has recovered); titrate to target trough concentrations. Adjunctive therapy with corticosteroids is recommended early post-transplant. I.V. route should only be used in patients not able to take oral medications and continued only until oral medication can be tolerated; anaphylaxis has been reported with I.V. administration. If switching from I.V. to oral, the oral dose should be started 8-12 hours after stopping the infusion.

#### **-Liver transplant:**

-Oral: Immediate release: Initial: 0.1-0.15 mg/kg/day in 2 divided doses, given every 12 hours (titrate to target trough concentrations)

-I.V.: Initial: 0.03-0.05 mg/kg/day as a continuous infusion

**-Heart transplant:** Use in combination with azathioprine or mycophenolate mofetil is recommended.

-Oral: Immediate release: Initial: 0.075 mg/kg/day in 2 divided doses, given every 12 hours (titrate to target trough concentrations)

-I.V.: Initial: 0.01 mg/kg/day as a continuous infusion

**-Kidney transplant:** Use in combination with azathioprine or mycophenolate mofetil is recommended. **Note:** African-American patients may require larger doses to attain trough concentration.

Oral:

*U.S. labeling:*

- Immediate release (Hecoria, Prograf): Initial: 0.2 mg/kg/day in combination with azathioprine or 0.1 mg/kg/day in combination with mycophenolate mofetil; titrate to target trough concentrations. Administer in 2 divided doses, given every 12 hours.
- Extended release (Astagraf XL):
- With basiliximab induction (prior to or within 48 hours of transplant completion): 0.15 mg/kg once daily (in combination with corticosteroids and mycophenolate); titrate to target trough concentrations
- Without basiliximab induction: Preoperative dose (administer within 12 hours prior to reperfusion): 0.1 mg/kg
- Without basiliximab induction: Postoperative dosing (administer at least 4 hours after preoperative dose and within 12 hours of reperfusion): 0.2 mg/kg once daily (in combination with corticosteroids and mycophenolate); titrate to target trough concentrations
- Conversion from I.V. to extended release: Administer the first oral extended release dose 8-12 hours after discontinuation of I.V. tacrolimus

*Canadian labeling:*

- Immediate release (Prograf): Initial: 0.2-0.3 mg/kg/day in 2 divided doses, given every 12 hours in combination with corticosteroids and other immunosuppressive agents; titrate to target trough concentrations
- Extended release (Advagraf): Initial: 0.15-0.2 mg/kg once daily; titrate to target trough concentrations. Administer in combination with corticosteroids and mycophenolate mofetil (MMF) in *de novo* kidney transplant recipients. Antibody induction therapy should also be used.
- Conversion from immediate release to extended release: Initiate extended release treatment using previously established total daily dose of immediate release. Administer once daily.

I.V.: Initial: 0.03-0.05 mg/kg/day as a continuous infusion

**-Graft-versus-host disease (GVHD) (unlabeled use):**

*Prevention:*

- Oral: Convert from I.V. to immediate release oral dose (1:4 ratio): Multiply total daily I.V. dose times 4 and administer in 2 divided oral doses per day, every 12 hours (Uberti, 1999; Yanik, 2000).
- I.V.: Initial: 0.03 mg/kg/day (based on lean body weight) as continuous infusion. Treatment should begin at least 24 hours prior to stem cell infusion and continued only until oral medication can be tolerated (Przepiorka, 1999; Yanik, 2000).

*Treatment:*

- Oral: Immediate release: 0.06 mg/kg twice daily (Furlong, 2000; Przepiorka, 1999)
- I.V.: Initial: 0.03 mg/kg/day (based on lean body weight) as continuous infusion (Furlong, 2000; Przepiorka, 1999)

**-Rheumatoid arthritis:** Canadian labeling (not in U.S. labeling): Oral: Immediate release: 3 mg once daily; carefully monitor serum creatinine during therapy

## **Geriatric**

Refer to adult dosing.

## **Renal Impairment**

- Evidence suggests that lower doses should be used; patients should receive doses at the lowest value of the recommended I.V. and oral dosing ranges; further reductions in dose below these ranges may be required. May also require dose reductions due to nephrotoxicity.
- Kidney transplant: Tacrolimus therapy in patients with postoperative oliguria should begin no sooner than 6 hours and within 24 hours (immediate release) or 48 hours (extended release) post-transplant, but may be delayed until renal function displays evidence of recovery.
- Hemodialysis: Not removed by hemodialysis; supplemental dose is not necessary.
- Peritoneal dialysis: Significant drug removal is unlikely based on physiochemical characteristics.

## **Hepatic Impairment**

Use of tacrolimus in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole blood levels of tacrolimus. The presence of moderate-to-severe hepatic dysfunction (serum bilirubin >2 mg/dL; Child-Pugh score  $\geq 10$ ) appears to affect the metabolism of tacrolimus. The half-life of the drug was prolonged and the clearance reduced after I.V. administration. The bioavailability of tacrolimus was also increased after oral administration. The higher plasma concentrations as determined by ELISA, in patients with severe hepatic dysfunction are probably due to the accumulation of metabolites of lower activity. These patients should be monitored closely and dosage adjustments should be considered. Some evidence indicates that lower doses could be used in these patients.

## **COMMON SIDE EFFECT:**

**$\geq 15\%$ :**

- Cardiovascular: Hypertension (13% to 62%), edema (peripheral 11% to 36%), chest pain (19%), edema (18%), pericardial effusion (heart transplant 15%)
- Central nervous system: Headache (24% to 64%), insomnia (30% to 64%), pain (24% to 63%), fever (19% to 48%), postprocedural pain (kidney transplant 29%), dizziness (19%)
- Dermatologic: Pruritus (15% to 36%), rash (10% to 24%)
- Endocrine & metabolic: New-onset diabetes after transplant (75% kidney transplant), hypophosphatemia (28% to 49%), hypomagnesemia (16% to 48%), hyperglycemia (21% to 47%), hyperkalemia (13% to 45%), hyperlipemia (10% to 31%), hypokalemia (13% to 29%), diabetes mellitus (24% to 26%), post-transplant diabetes mellitus (heart transplant 13% to 22%; kidney transplant 20%; liver transplant 11% to 18%)
- Gastrointestinal: Diarrhea (25% to 72%), abdominal pain (29% to 59%), nausea (32% to 46%), constipation (23% to 36%), anorexia (7% to 34%), vomiting (14% to 29%), dyspepsia (18% to 28%)
- Genitourinary: Urinary tract infection (16% to 34%)
- Hematologic: Anemia (5% to 50%), leukopenia (13% to 48%), leukocytosis (8% to 32%), thrombocytopenia (14% to 24%)
- Hepatic: Liver function tests abnormal (6% to 36%), ascites (7% to 27%)
- Local: Incision site complication (kidney transplant 28%)

- Neuromuscular & skeletal: Tremor (15% to 56%; heart transplant 15%), weakness (11% to 52%), paresthesia (17% to 40%), back pain (17% to 30%), arthralgia (25%)
- Renal: Abnormal kidney function (36% to 56%), creatinine increased (23% to 45%), BUN increased (12% to 30%), oliguria (18% to 19%)
- Respiratory: Atelectasis (5% to 28%), pleural effusion (30% to 36%), dyspnea (5% to 29%), cough increased (18%), bronchitis (17%)
- Miscellaneous: Infection (24% to 45%), CMV infection (heart transplant 32%), graft dysfunction (kidney transplant 24%)

**PREGNANCY RISK FACTORS: C**