SIROLIMUS

CLASS: Immunosuppressant Agent; mTOR Kinase Inhibitor

INDICATIONS: Prophylaxis of organ rejection in patients receiving renal transplants

AVAILABLE DOSAGE FROM THE HOSPITAL:

SIROLIMUS 1MG TABLET

DOSAGE:

-Low-to-moderate immunologic risk renal transplant patients:

Oral:

- <40 kg: Loading dose: 3 mg/m^2 on day 1, followed by maintenance dosing of 1 mg/m^2 once daily
- ≥40 kg: Loading dose: 6 mg on day 1; maintenance: 2 mg once daily

-High immunologic risk renal transplant patients: Oral: Loading dose: Up to 15 mg on day 1; maintenance: 5 mg/day; obtain trough concentration between days 5-7 and adjust accordingly. Continue concurrent cyclosporine/sirolimus therapy for 1 year following transplantation. Further adjustment of the regimen must be based on clinical status.

-Dosage adjustment:

Sirolimus dosages should be adjusted to maintain trough concentrations within desired range based on risk and concomitant therapy. Maximum daily dose: 40 mg. Dosage should be adjusted at intervals of 7-14 days to account for the long half-life of sirolimus. In general, dose proportionality may be assumed. New sirolimus dose **equals** current dose **multiplied by** (target concentration **divided by** current concentration). **Note:**If large dose increase is required, consider loading dose calculated as:

Loading dose **equals (new maintenance dose **minus** current maintenance dose) **multiplied by** 3

**Maximum dose in 1 day: 40 mg; if required dose is >40 mg (due to loading dose), divide loading dose over 2 days. Whole blood concentrations should not be used as the sole basis for dosage adjustment (monitor clinical signs/symptoms, tissue biopsy, and laboratory parameters).

-Maintenance therapy after withdrawal of cyclosporine: Cyclosporine withdrawal is not recommended in high immunological risk patients. Following 2-4 months of combined therapy, withdrawal of cyclosporine may be considered in low-to-moderate immunologic risk patients. Cyclosporine should be discontinued over 4-8 weeks, and a necessary increase in the dosage of sirolimus (up to fourfold) should be anticipated due to removal of metabolic inhibition by cyclosporine and to maintain adequate immunosuppressive effects. Dose-adjusted trough target concentrations are typically 16-24 ng/mL for the first year post-transplant and 12-20 ng/mL thereafter (measured by chromatographic methodology).

-Graft-versus-host disease (GVHD): Oral:

- **GVHD prophylaxis (unlabeled use):** 12 mg loading dose on day -3, followed by 4 mg daily (target trough level: 3-12 ng/mL); taper off after 6-9 months (Armand, 2008; Cutler, 2007)
- **Treatment of refractory acute GVHD (unlabeled use):** 4-5 mg/m^2 for 14 days (no loading dose) (Benito, 2001)
- **Treatment of chronic GVHD (unlabeled use):** 6 mg loading dose, followed by 2 mg daily (target trough level: 7-12 ng/mL) for 6-9 months (Couriel, 2005)

-Heart transplantation (unlabeled use): Oral: **Note:** The use of sirolimus in the immediate post-cardiac transplant period (ie, *de novo* heart transplant) as a primary immunosuppressant has fallen out of favor due to adverse effects (eg, impaired wound healing and infection); however, patients may be converted to sirolimus from a calcineurin inhibitor (after at least 6 months from time of transplant [Costanzo, 2010]) or may have sirolimus added to a calcineurin inhibitor to prevent or minimize further transplant related vasculopathy or renal toxicity due to calcineurin inhibitor use.

- *Conversion from a calcineurin inhibitor (CNI) (ie, cyclosporine, tacrolimus):* Reduce cyclosporine by 25 mg twice daily or tacrolimus by 1 mg twice daily followed by initiation of sirolimus 1 mg once daily; adjust sirolimus dose to target trough level of 8-14 ng/mL, withdraw CNI, repeat biopsy 2 weeks after CNI withdrawal (Topilsky, 2012). Alternatively, maintain CNI concentrations and initiate sirolimus 1 mg once daily for 1 week; adjust sirolimus to target trough levels of 10-15 ng/mL over 2 weeks, then reduce CNI to target 50% of therapeutic concentrations and after 2 weeks evaluate for rejection. If no rejection, continue same regimen for an additional month, then reduce CNI to 25% of therapeutic concentrations with repeat biopsy 2 weeks later; if no rejection, may discontinue CNI after 2 weeks and continue to maintain sirolimus trough levels of 10-15 ng/mL (usual doses required to maintain target levels: 1-8 mg daily) (Kushwaha, 2005).
- *Conversion from antiproliferative drug (ie, azathioprine or mycophenolate) while maintaining calcineurin inhibitor:* Upon discontinuation of antiproliferative, administer sirolimus 6 mg loading dose followed by 2 mg once daily titrated to a target trough level of 4-15 ng/mL (Mancini, 2003) or 4-12 ng/mL per ISHLT recommendations (Costanzo, 2010).

-Renal angiomyolipoma or lymphangioleiomyomatosis (unlabeled use): Oral: Initial: 0.5 mg/m^2 once daily titrated to a target trough level of 3-6 ng/mL (may increase to target trough level of 6-10 ng/mL if <10% reduction in lesion diameters at 2 months) for 2 years (Davies, 2011) **or** Initial: 2 mg once daily titrated to a target trough level of 5-15 ng/mL for 1 year (McCormack, 2011)

Geriatric

Refer to adult dosing.

Renal Impairment :

No dosage adjustment (in loading or maintenance dose) necessary. However, adjustment of regimen (including discontinuation of therapy) should be considered when used concurrently with cyclosporine and elevated or increasing serum creatinine is noted.

Hepatic Impairment:

Loading dose: No dosage adjustment required.

Maintenance dose:

Mild-to-moderate hepatic impairment (Child-Pugh classes A and B): Reduce maintenance dose by ~33%.

Severe hepatic impairment (Child-Pugh class C): Reduce maintenance dose by ~50%.

COMMON SIDE EFFECTS:

>20%:

- Cardiovascular: Peripheral edema (54% to 58%), hypertension (45% to 49%), edema (18% to 20%)
- Central nervous system: Headache (34%), pain (29% to 33%), insomnia (13% to 22%)
- Dermatologic: Acne (22%)
- Endocrine & metabolic: Hypertriglyceridemia (45% to 57%), hypercholesterolemia (43% to 46%)
- Gastrointestinal: Constipation (36% to 38%), abdominal pain (29% to 36%), diarrhea (25% to 36%), nausea (25% to 31%)
- Genitourinary: Urinary tract infection (26% to 33%)
- Hematologic: Anemia (23% to 33%), thrombocytopenia (14% to 30%)
- Neuromuscular & skeletal: Arthralgia (25% to 31%)
- Renal: Serum creatinine increased (39% to 40%)

PREGNANCY RISK FACTORS: C