CYCLOSPORINE

CLASS: Calcineurin Inhibitor; Immunosuppressant Agent

INDICATIONS:

Cyclosporine modified:

Transplant rejection prophylaxis: Prophylaxis of organ rejection in kidney, liver, and heart transplants (has been used with azathioprine and/or corticosteroids)

Rheumatoid arthritis: Treatment of severe, active rheumatoid arthritis (RA) not responsive to methotrexate alone

Psoriasis: Treatment of severe, recalcitrant plaque psoriasis in nonimmunocompromised adults unresponsive to or unable to tolerate other systemic therapy

Cyclosporine non-modified: Transplant rejection (prophylaxis/treatment): Prophylaxis of organ rejection in kidney, liver, and heart transplants (has been used with azathioprine and/or corticosteroids; treatment of chronic organ rejection)

AVAILABLE DOSAGE FROM THE HOSPITAL:

CYCLOSPORINE  25MG CAP
CYCLOSPORINE  50MG CAP
CYCLOSPORINE 0.05% OPHTHALMIC EMULSION
CYCLOSPORINE 100MG CAP
CYCLOSPORINE 100MG ORAL-SOLUTION
CYCLOSPORINE 50MG/ML 5MLAMP

TRADE NAMES:

DOSAGE:

• Dosing Adult:
Neoral/Gengraf and Sandimmune are not bioequivalent and cannot be used interchangeably.

**Newly-transplanted patients:** Adjunct therapy with corticosteroids is recommended. Initial dose should be given 4-12 hours prior to transplant or may be given postoperatively; adjust initial dose to achieve desired plasma concentration.

Oral: Dose is dependent upon type of transplant and formulation:

Cyclosporine (modified):

Renal: 9 ± 3 mg/kg/day, divided twice daily
Liver: 8 ± 4 mg/kg/day, divided twice daily
Heart: 7 ± 3 mg/kg/day, divided twice daily

Cyclosporine (non-modified): Initial doses of 10-14 mg/kg/day have been used for renal transplants (the manufacturer’s labeling includes dosing from initial clinical trials of 15 mg/kg/day [range: 14-18 mg/kg/day]; however, this higher dosing level is rarely used any longer). Continue initial dose daily for 1-2 weeks; taper by 5% per week to a maintenance dose of 5-10 mg/kg/day; some renal transplant patients may be dosed as low as 3 mg/kg/day

**Note:** When using the non-modified formulation, cyclosporine levels may increase in liver transplant patients when the T-tube is closed; dose may need decreased

I.V.: Cyclosporine (non-modified): Manufacturer’s labeling: Initial dose: 5-6 mg/kg/day or one-third of the oral dose as a single dose, infused over 2-6 hours; use should be limited to patients unable to take capsules or oral solution; patients should be switched to an oral dosage form as soon as possible

**Note:** Many transplant centers administer cyclosporine as "divided dose" infusions (in 2-3 doses/day) or as a continuous (24-hour) infusion; dosages range from 3-7.5 mg/kg/day. Specific institutional protocols should be consulted.

**Note:** Conversion to cyclosporine (modified) from cyclosporine (non-modified): Start with daily dose previously used and adjust to obtain preconversion cyclosporine trough concentration. Plasma concentrations should be monitored every 4-7 days and dose adjusted as necessary, until desired trough level is obtained. When transferring patients with previously poor absorption of cyclosporine (non-modified), monitor trough levels at least twice weekly (especially if initial dose exceeds 10 mg/kg/day); high plasma levels are likely to occur.
**Rheumatoid arthritis:** Oral: Cyclosporine (modified): Initial dose: 2.5 mg/kg/day, divided twice daily; salicylates, NSAIDs, and oral glucocorticoids may be continued (refer to Drug Interactions); dose may be increased by 0.5-0.75 mg/kg/day if insufficient response is seen after 8 weeks of treatment; additional dosage increases may be made again at 12 weeks (maximum dose: 4 mg/kg/day). Discontinue if no benefit is seen by 16 weeks of therapy.

*Note:* Increase the frequency of blood pressure monitoring after each alteration in dosage of cyclosporine. Cyclosporine dosage should be decreased by 25% to 50% in patients with no history of hypertension who develop sustained hypertension during therapy and, if hypertension persists, treatment with cyclosporine should be discontinued.

**Psoriasis:** Oral: Cyclosporine (modified): Initial dose: 2.5 mg/kg/day, divided twice daily; dose may be increased by 0.5 mg/kg/day if insufficient response is seen after 4 weeks of treatment; additional dosage increases may be made every 2 weeks if needed (maximum dose: 4 mg/kg/day). Discontinue if no benefit is seen by 6 weeks of therapy. Once patients are adequately controlled, the dose should be decreased to the lowest effective dose. Doses <2.5 mg/kg/day may be effective. Treatment longer than 1 year is not recommended.

*Note:* Increase the frequency of blood pressure monitoring after each alteration in dosage of cyclosporine. Cyclosporine dosage should be decreased by 25% to 50% in patients with no history of hypertension who develop sustained hypertension during therapy and, if hypertension persists, treatment with cyclosporine should be discontinued.

**Acute graft versus host disease (GVHD), prevention (unlabeled use):** Adults: I.V. followed by oral:

Initial: I.V.: 3 mg/kg/day 1 day prior to transplant; may convert to oral therapy when tolerated; titrate dose to appropriate cyclosporine trough concentration (in combination with methotrexate); taper per protocol (refer to specific references for tapering and target trough details); discontinue 6 months post transplant in the absence of acute GVHD (Ratanatharathorn, 1998; Ruutu, 2013; Storb, 1986a; Storb, 1986b)

or
Initial: I.V.: 5 mg/kg (continuous infusion over 20 hours) each day for 6 days (loading dose) starting 2 days prior to transplant, then 3 mg/kg over 20 hours each day for 11 days starting on post transplant day 4, then 3.75 mg/kg over 20 hours each day for 21 days starting on day 15, then oral (in 2 divided daily doses): 10 mg/kg/day days 36 to 83, then 8 mg/kg/day days 84 to 97, then 6 mg/kg/day days 98 to 119, then 4 mg/kg/day days 120 to 180, then discontinue (in combination with methotrexate +/- corticosteroid) (Chao, 1993; Chao, 2000)

**Focal segmental glomerulosclerosis (unlabeled use):** Oral: Initial: 3.5-5 mg/kg/day divided every 12 hours (in combination with oral prednisone) (Braun, 2008; Cattran, 1999)

**Lupus nephritis (unlabeled use):** Oral: Initial: 4 mg/kg/day for 1 month (reduce dose if trough concentrations >200 ng/mL); reduce dose by 0.5 mg/kg every 2 weeks to a maintenance dose of 2.5-3 mg/kg/day (Moroni, 2006)

**Ulcerative colitis, severe (steroid-refractory) (unlabeled use):**

I.V.: Cyclosporine (non-modified): 2-4 mg/kg/day, infused continuously over 24 hours. (Lichtiger, 1994; Van Assche, 2003). Note: Some studies suggest no therapeutic difference between low-dose (2 mg/kg) and high-dose (4 mg/kg) cyclosporine regimens (Van Assche, 2003).

Oral: Cyclosporine (modified): 2.3-3 mg/kg every 12 hours (De Saussure, 2005; Weber, 2006)

**Note:** Patients responsive to I.V. therapy should be switched to oral therapy when possible

- **Dosing: Geriatric**

Refer to adult dosing. Sandimmune and Neoral/Gengraf are not bioequivalent and cannot be used interchangeably.

- **Dosing: Renal Impairment**

For severe psoriasis:

**Serum creatinine levels ≥25% above pretreatment levels:** Take another sample within 2 weeks; if the level remains ≥25% above pretreatment levels, decrease dosage of cyclosporine (modified) by 25% to 50%. If two dosage adjustments do not reverse the increase in serum creatinine levels, treatment should be discontinued.
Serum creatinine levels ≥50% above pretreatment levels: Decrease cyclosporine dosage by 25% to 50%. If two dosage adjustments do not reverse the increase in serum creatinine levels, treatment should be discontinued.

**Hemodialysis:** Supplemental dose is not necessary.

**Peritoneal dialysis:** Supplemental dose is not necessary

- **Dosing: Hepatic Impairment**
  
  Mild-to-moderate impairment: No dosage adjustment provided in the manufacturer’s labeling; monitor blood concentrations.
  
  Severe impairment: Metabolism is extensively hepatic (exposure is increased); monitor blood concentrations; may require dose reduction.

**COMMON SIDE EFFECT:** Adverse reactions reported with systemic use, including rheumatoid arthritis, psoriasis, and transplantation (kidney, liver, and heart). Percentages noted include the highest frequency regardless of indication/dosage. Frequencies may vary for specific conditions or formulation.

>10%:

**Cardiovascular:** Hypertension (8% to 53%), edema (5% to 14%)

**Central nervous system:** Headache (2% to 25%)

**Dermatologic:** Hirsutism (21% to 45%), hypertrichosis (5% to 19%)

**Endocrine & metabolic:** Triglycerides increased (15%), female reproductive disorder (9% to 11%)

**Gastrointestinal:** Nausea (23%), diarrhea (3% to 13%), gum hyperplasia (2% to 16%), abdominal discomfort (<1% to 15%), dyspepsia (2% to 12%)

**Neuromuscular & skeletal:** Tremor (7% to 55%), paresthesia (1% to 11%), leg cramps/muscle contractions (2% to 12%)

**Renal:** Renal dysfunction/nephropathy (10% to 38%), creatinine increased (16% to ≥50%)

**Respiratory:** Upper respiratory infection (1% to 14%)

**Miscellaneous:** Infection (3% to 25%)
PREGNANCY RISK FACTORS: C