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